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ANNALS OF
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VOLUME 27 AUGUST, 1947 NUMBER 2

THE RESPONSIBILITIES OF THE INTERNIST *

By DAVID P. BARR, F.A.C.P., *New York, N. Y.*

FELLOWS OF THE AMERICAN COLLEGE OF PHYSICIANS:

By custom I am permitted as your President to address you on this occasion of the Annual Convocation, and in the few moments at my disposal should like to outline a few of the accomplishments of the College and also to indicate some of the responsibilities which we as Internists may assume in our development. Before doing so, however, I should be neglectful of opportunity if I failed to express to you my profound appreciation of the honor of being allowed during the past year to serve in this high office. Like my distinguished predecessors, I have done my best to advance the purposes of the College. I realize that the little I have accomplished during my term is inadequate evidence of my estimation of the privilege.

The American College of Physicians is the organization of the internists of North America. During the 30 years of its existence it has been responsible for many developments and advances. In its annual and regional meetings it has furnished forum and assembly to consider problems of mutual interest and to foster acquaintance of internists from different districts and different conditions of practice. In its Annals, now one of the greater journals of internal medicine, it has been able to publish not only the best of our scientific proceedings but also to make known many of the activities of the College. The American Board of Internal Medicine which was initiated by the College has been useful in establishing standards for practice. Other educational activities of the College have been numerous. Most important perhaps have been the research fellowships for the encouragement and educational opportunity of young men who wish to become internists. The John Phillips Memorial Award has made it possible to honor each year outstandingly significant work in the field of internal medicine or its ancillary sciences and the convocational lectureship has provided for each annual meeting a speaker of national importance.

* Presidential Address delivered at the Convocation of the American College of Physicians, Chicago, April 30, 1947.

During the past few years, postgraduate courses of increasing variety have been offered. It is well known to most of you that much of the impetus for this type of instruction in the College came from our former president, Dr. James D. Bruce, whose death last September has saddened us all. Later in the autumn of 1946 it was made known that Dr. Bruce had left a substantial part of his estate to the American College of Physicians and had provided, among other things, for the establishment of a lectureship to honor Dr. Alfred Stengel and for an award of merit for outstanding contribution in Public Health and Preventive Medicine to be known as the James D. Bruce Award in Preventive Medicine, this to be signalized by a medal which the Board of Regents is now having prepared. Dr. Bruce's wise bequest has thus opened the way for further extension of the educational activities of the College and has made possible the beginning of greater emphasis in our meetings on the preventive aspects of disease.

We can take pride in the accomplishments of our organization. It has been more than an instrument for raising the standards of practice and it has gradually assumed an outstanding rôle in the education of internists. In congratulating ourselves, however, we should examine the situation broadly and inquire whether the teaching we are now fostering offers in scope and content the best opportunities for future development.

Consideration of this problem raises again the question which has been posed so many times at these convocations. What, after all, is an internist? You will remember that this was the subject of a most entertaining presidential address by Perry Pepper who concluded that an internist is a creature that cannot be defined. Without attempting to reëmphasize the difficulties of definition or to reëxamine all the facets of a complex question, it may be assumed that an internist must be both an expert diagnostician and an expert therapist. He must be a master of the method of case-study, a discriminating practitioner of all the technics and skills which may be used to label and classify disease, to relate the symptoms found at the bedside to anatomical deviations, to specifically harmful agents, to the functional capacity of organs, and to chemical abnormalities in the internal environment of the body. He must pride himself on being a scientist at the bedside—on the precise application of his many resources, his physical examination, his discriminating use of the roentgen-ray, his discernment in the selection of chemical and biological tests, and his skill in the interpretation of the electrocardiogram. He must school himself to analyze and synthesize all that he has observed and discovered into a correct and defensible diagnosis of a condition to which he can apply an antibiotic, a hormone, a vitamin, or some other precise remedy. In pursuing this ideal he is in effect extending the dream of Thomas Sydenham that sufficient observation and study will enable the physician to describe and classify all ills and in time to find a specific for each.

These scientific methods employed by internists have been instrumental in the early recognition and satisfactory control of a great number of clinical conditions. They have been helpful in establishing greater freedom from

infection, better nutrition and better health than has been known before. To all of us who use them, however, their limitations are obtrusive. In spite of their increasing complexity and scientific exactitude they may fail to acquaint us with the real problems of the man or woman who is sick. Many times indeed the routine questioning and testing become so elaborate and time-consuming that there is little opportunity for the patient to give or for the internist to hear an unimpeded and uninterrupted account of the illness. It appears that often in the complicated analysis the true goal may be lost. Pope expressed the thought when he said,

> "Like following life, through creatures you dissect,
> You lose it the moment you detect."

There is also a question whether anxiety to recognize early organic disease may make one oblivious to the danger of producing invalidism and neurosis, whether chagrin over failure to hear a low-pitched murmur or to feel a palpable spleen is matched by the discomfiture of missing completely the personality of the patient, his hopes and fears, his hates and loves, his obsessions and frustrations, or the indelible imprint which his disease has made on his attitudes and motivations.

If, however, the objectives of the internist are correct diagnosis and optimal treatment these considerations are matters of much more than academic interest, for they are essential to the correct evaluation of symptoms and to the estimate of hypotheses upon which diagnoses and subsequent treatment are based.

The influence which emotions may have on bodily functions has always been realized. To some degree everyone knows the changes that grief, fright, horror, or disgust may accomplish. Great literature is replete with penetrating observations which mirror both the phenomena and their degree.

> "I could a tale unfold whose lightest word
> Would harrow up thy soul, freeze thy young blood,
> Make thy two eyes like stars start from their spheres
> Thy knotted and combined locks to stand on end
> Like quills upon the fretful porpentine."

Everyone recognizes the influence of emotion upon the flow of tears, the secretion of sweat, the color of the face, the temperature of the hands. Everyone knows the racing heart of excitement, the gasp of horror, the panting of passion, the polyuria of suspense, and the incontinence of panic.

When one recalls how universally the changes accompanying emotion have been noted, it is surprising that in the past they have been subjected to so little critical analysis. For instance, while it has been known that in those who are embarrassed or resentful the skin may blush, and that in those who are apprehensive or frightened it may become pallid, there has been little curiosity concerning the behavior under similar circumstances of the mucous membranes of the mouth, the nose, the gastric mucosa, the intestinal tract, the pelves of the kidney and the urinary bladder. Nor has there been sufficient

emphasis upon the possibility that while the face might become flushed or pallid without serious consequences, the same might not be true of frequently repeated circulatory changes in body surfaces that were concerned with digestion, assimilation, elimination or other special function. Enthusiasm for chemical and physical investigation of disease has left little time for inquiry concerning the precise effects of the emotions and it is only in recent years that systematic studies along these lines have been attempted.

Such researches, however, have already transformed our concepts of certain diseases, previously regarded as organic and therapeutically susceptible to more or less specific remedies. Most strikingly they have aided us in the understanding and interpretation of gastrointestinal conditions. The classical studies of Harold Wolff and his associates have shown that embarrassment or resentment may cause in the stomach a flushing, a hyperemia and at the same time an increase in secretion of acid; that when these emotions are continuous or often repeated, erosions of the mucosa may occur and that finally actual ulcerations may develop with symptoms indistinguishable from peptic ulcer. Of equal significance were their observations that in the same individual, fear and dread may be accompanied by abnormal pallor of the gastric mucosa with diminution or temporarily complete absence of gastric secretion and with loss of appetite and disgust for food. Similar changes have been seen in the nasal mucous membrane where resentment and embarrassment may produce hyperemia and excessive secretion while fear results in pallor and drying of secretions.

These observations must be regarded as only preliminary and there is little reason to suppose that the responses to emotion of other tissues and organs are less significant. Much evidence is already at hand to indicate that such diverse conditions as asthma, hypertension, thyrotoxicosis, ulcerative colitis and glaucoma have as a part of the symptom complex an emotional component which is significant both etiologically and symptomatically.

In evaluating these studies it must be constantly kept in mind that the reactions to situations cannot be separated sharply into emotional and organic components. In a resentful man the effect of the situation which rouses his resentment will be portrayed in his nose, his stomach, his urinary tract, his posture, and the sour look on his face. The entire organism reacts to environment which it has interpreted as threatening.

Such considerations are of the utmost significance in the daily work of internists. Anatomical and functional organic changes reflecting the play of emotions affect every human being, the sound and strong as well as the sick and weak. Recognizable organic diseases such as diabetes, pernicious anemia, tuberculosis or syphilis do not remove the patient from the category of those who suffer adversely from emotional reactions. Indeed organic disease may exaggerate anxieties, fears and obsessions. On the other hand, freedom from disease and excellent nutrition will not necessarily bring happiness, contentment or freedom from psychological deterioration or emotional disaster.

If we as internists regard the matter soberly, it is apparent that no illness can be correctly formulated or treated unless the patient's environment and his attitudes and reactions to it are taken into account; furthermore that our physical and chemical methods of examination as well as our specifics are inadequate in the care of a vast number of people.

The apparent lack of parallelism between the state of physical well being and emotional and psychological reactions, as well as the inadequacy of our diagnostic and therapeutic resources, appeared most clearly during the stress of war. In spite of incredible hardships and exposures, the well being of our troops as measured by physical means was unprecedented. Under most circumstances there was excellent nutrition and unusual freedom from infection. The majority who became ill were not physically defective or diseased. They came from the ranks of those who were emotionally infirm or maladjusted; of those whose motivation was faulty and who lacked faith and dedication to the purposes of the war. No chemical or physical tests could reveal the depth of their misery, no *specifics* of modern medicine could give them faith, conviction, or courage.

Mature consideration of the situation indicates that this problem which now looms so large in medical practice is but a segment of one of the most cogent realities of our time. Science and scientific methods which can provide useful and comforting things such as freedom from infection, good nutrition, alleviation of pain, and prolongation of life, cannot control fear, or shame, or grief; cannot establish purpose or dedication either for well or suffering human beings; cannot instil faith, hope, love, equanimity, or the other values that make life worth living.

All scientists are in need of Humanism which may be regarded as realization and affirmation of the importance of Man's spiritual values. Physicians whose science is applied to the alleviation of suffering can never dispense with this concept. The internist may remain scientist only so long as his patient has recognizable anatomical and chemical abnormalities which are susceptible to treatment by specific procedures. More often than not, as Alan Gregg has said, ". . . a miraculous moment comes when the doctor becomes the treatment. And it is just there that Science like a relay runner must pass the torch to Humanism."

In medicine as in the world in general, the last few years have been marked by a renewed respect for the humanistic approach. Many factors have contributed to this end. Closer scrutiny of the effects of emotions has pointed the way to a greater appreciation of their clinical significance. The horrors of war and the worldwide misery which has accompanied and followed it have made men realize the limitations of current scientific methods and applications. Contemplation has brought again the realization of the true physician-patient relation which is not scientific but humanistic. The thoughts of a layman of 1850 are relevant. Nathaniel Hawthorne is writing of Roger Chillingworth, the physician of The Scarlet Letter, "He deemed it essential, it would seem, to know the man before attempting to do him good.

Whenever there is a heart and an intellect the diseases of the physical frame are tinged with the peculiarities of these. . . . The man of skill, the kind and friendly physician strove to go deep into his patients' bosom, delving among his principles, prying into his recollections, and probing everything with a cautious touch like a treasure seeker in a dark cavern. . . . If he (the physician) possess native sagacity and a nameless something more—let us call it intuition, if he show no intrusive egotism, nor disagreeably prominent characteristics of his own; if he have the power, which must be born with him, to bring his mind into such affinity with his patient's that this last shall unawares have spoken what he imagines himself only to have thought; if such revelations be received without tumult and acknowledged not so often by an uttered sympathy as by silence, an inarticulate breath and here and there a word, to indicate that all is understood; if to these qualifications of confidant be joined the advantages afforded by his recognized character as a physician then at some inevitable moment will the soul of the sufferer be dissolved and flow forth in a dark but transparent dream bringing all its mysteries into the daylight."

Nothing could express more vividly the humanistic approach. No post-war modern with the new light of psychosomatic medicine in his eye could indicate more vividly the limitations of scientific medicine as it is now conceived.

It is deplorable that this most significant aspect of medical practice has been so largely omitted from the training and constructive thought of the internist. In medical schools of the past and even in those of today the emphasis has been upon the recognition and treatment of organic disease or on systemic conditions in which chemical or metabolic defects have been clearly demonstrable. The examinations of the American Board of Internal Medicine have been notably free of any questions concerning emotional factors or life situations in the causation of disease. The programs of the annual and regional meetings of the College have been devoted with few exceptions to physical factors and to pathology which is dependent upon anatomical or chemical deviations.

An attitude is gaining ground among the profession as well as with the laity that if a man has no demonstrable defect and still persists in being ill, he should consult a psychiatrist. Or since psychiatrists are rare and such patients seem to be innumerable, he should perhaps try to find someone who for want of a better term has been called a specialist in psychosomatic medicine, and who has become especially interested in the relationships and interplay of organic and emotional disease.

Such an attitude may have some justification in expediency to meet existing conditions, but can do little toward the final solution of the problem. Psychosomatic medicine is medicine itself. The rôle of humanist cannot be assigned to any one group, whether its members be called psychiatrists, psychosomaticists, or priests. The study of man and his values is at least as much a part of internal medicine as physiology, chemistry, or anatomy.

Fundamental concepts which involve or modify our understanding of all disease can never be regarded as clinical specialties.

It must not be expected that we as internists can assume this obligation at once or in full measure. There are many obstacles. We who have received our training in the past have had our attention focused upon the recognition and treatment of organic and mechanical abnormalities. We have been obsessed with the fear of missing the presence of serious or potentially serious anatomical or chemical disease. Intellectually we have been occupied with the relationship of clinical signs and anatomical deviations, with the correction of chemical defects and with the search and application of specifics. We have become burdened with a time-consuming and elaborate ritual to accomplish these purposes. While all of this is praiseworthy it is not enough if in the process we have lost the listening ear and our contacts with patients as people, or if we attempt to make diagnoses and decisions without consideration of personal problems, interpersonal relationships, and life situations in family, occupation and community.

It is by no means implied that all internists are involved in these defects. Osler, Francis Peabody, and many other of our predecessors were great humanists who in being so never lost their respect for science. There are many among us today and not a few of our own number in this College who while applying admirably the methods of science, realize their limitations and in their daily rounds practice a liberal humanism to the great benefit of their patients. The implication is simply that we internists as a group have become perhaps too fascinated with an approach which cannot solve all of the problems of any of our patients or any of the problems of others. Such concentration has too often resulted in a failure to appreciate the realities of the physician-patient relationship.

No originality can be claimed for this thesis. One may hear it better from Plato: ". . . so neither ought you to attempt to cure the body without the soul; and this is the reason why the cure of many diseases is unknown to the physicians of Hellas, because they are ignorant of the whole which ought to be studied also; for the part can never be well unless the whole is well. . . . For this is the great error of our day in the treatment of the human body, that physicians separate the soul from the body."

In our development as internists and as a College intrusted in no small measure with the education of future physicians, not the least of our obligations should be an attempt to capture a proper balance between scientific study of physical defects and due regard for the emotional and psychological needs of our patients—to promote integration of Science and Humanism in the practice of our art.

CHRONIC LIVER DISEASE FOLLOWING INFECTIOUS HEPATITIS. I. ABNORMAL CONVALESCENCE FROM INITIAL ATTACK *

By HENRY G. KUNKEL, M.D., DANIEL H. LABBY, M.D., and CHARLES L. HOAGLAND,† M.D., *New York, N. Y.*

THE problem of the after-effects of infectious hepatitis is of particular importance at the present time because of the high incidence of this disease during the recent World War. It is now recognized that certain cases of this disease depart from the usual benign course and persist in showing signs and symptoms of liver insufficiency for months or even years following the initial attack. Weakness, fatigue, anorexia, liver tenderness, pain over the liver after exertion, and intolerance to fatty foods have been noted as the most prominent symptoms of this lingering type of hepatitis.[1, 2, 3, 4, 5, 6, 7]

Certain abnormalities in liver function have also been described in these patients. Elevation of the plasma bilirubin has been generally considered the most common aberration. Altschule and Gilligan[8] reported a 25 per cent incidence of hyperbilirubinemia in a group of healthy individuals who had had jaundice one to 29 years previously. Other workers[3, 4, 5, 9] found abnormal excretion of intravenously administered bilirubin, in both symptomatic and asymptomatic cases, following an earlier attack of infectious hepatitis. Barker and associates,[7] in their study of chronic hepatitis in the Mediterranean theatre during World War II, considered bromsulfalein retention the most useful liver function test. Recent reports[10, 11] have emphasized the sensitivity of the thymol turbidity reaction of the serum in detecting persistent liver disease.

The final outcome of cases with lingering hepatitis is not clear. Several workers[12, 13, 14, 15, 16] have described cirrhosis of the liver following infectious hepatitis, but the cases were few in number and usually in an older age group in which other factors, such as poor diet and alcoholism, may have been of importance. Neither the incidence nor the type of cirrhosis following infectious hepatitis is definitely known. A solution to the problem will probably depend upon the close observation and study of a large group of patients for a considerable period of time after their initial attack of infectious hepatitis. This paper deals with the early phase of such a study.

Three hundred and fifty Navy men were admitted to the Hospital of The Rockefeller Institute during the acute stage of infectious hepatitis. Because the men were young and had enjoyed previous good health, this group was

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From the U. S. Naval Research Unit at the Rockefeller Hospital and the Hospital of The Rockefeller Institute for Medical Research, New York, N. Y.
The Bureau of Medicine and Surgery of the U. S. Navy does not necessarily endorse the ideas set forth in this paper.
† Deceased, August 2, 1946.

particularly suited for a study of the chronic aspects of the disease. The diagnosis was easily confirmed in each case by a careful history, physical examination and selected tests of liver function. A minimum of complicating factors was encountered in the group.

The signs and symptoms of liver insufficiency displayed by each patient were carefully followed with special reference to their persistence or recrudescence during convalescence. As a supplement to the clinical observations, numerous laboratory tests were used. It was believed that by such a correlation early abnormalities in the course of the disease could be detected.

After a preliminary study of the results of various tests of liver function,[17] the following determinations were selected as most useful and were carried out at weekly intervals throughout the period of hospitalization:

Plasma Bilirubin: Method of Malloy and Evelyn,[18] including one-minute readings introduced by Ducci and Watson.[19]

Bromsulfalein Retention: Method of Rosenthal and White [20] modified for use of the Coleman Jr. spectrophotometer. Five mg. of bromsulfalein per kg. of body weight were injected and the per cent retention of the dye determined after 45 minutes.

Thymol Turbidity: Method of MacLagen with modification by Shank and Hoagland.[21, 11]

Other tests used at less regular intervals were the following:

Cholesterol: Free and total fractions, method of Schoenheimer and Sperry.[22]

Plasma Protein: Nesslerization technic from Army Medical Laboratory Manual.[23]

Hippuric Acid Synthesis: Method of Quick.[24]

Cephalin Flocculation: Modification of Hanger's method.[25]

Dragstedt and Mills [26] found that an elevated plasma bilirubin interfered with the function of the liver involved in the excretion of bromsulfalein. However, in following this group of patients, the determination of bromsulfalein retention was of value even in the presence of clinical icterus. The use of the spectrophotometer eliminated any interference in the laboratory estimation of the bromsulfalein level. In the average uncomplicated case of infectious hepatitis, the plasma bilirubin level and bromsulfalein retention were found to parallel each other closely during the recovery period of the disease (figure 1). Since a divergence in this close relationship was found to be a significant early indication of abnormal convalescence, simultaneous determinations of the two tests were carried out.

Two hundred and ninety of the 350 patients, or 83 per cent, recovered from the acute attack in less than three months, the average period of illness being 56 days. On admission to the hospital, all patients showed definite clinical icterus associated with varying degrees of anorexia, nausea, vomiting, and fever. These symptoms disappeared rapidly after admission and, at the

same time, plasma bilirubin, bromsulfalein retention, and thymol turbidity values showed a sharp fall. Figure 1 represents the normal convalescence observed in a typical case. The criteria for recovery included the disappearance of all symptoms and signs, and the presence of plasma bilirubin levels below 1 mg. per cent and bromsulfalein retention below 5 per cent following a 10-day test period of full activity.

In 60 of the 350 cases, or 17 per cent, recovery did not proceed in the manner just described and hospitalization for longer than three months was required. On the basis of the clinical course and the pattern of serial liver function tests in these cases, it was possible to distinguish the following groups: (1) simple relapse, symptomatic and asymptomatic, with recovery;

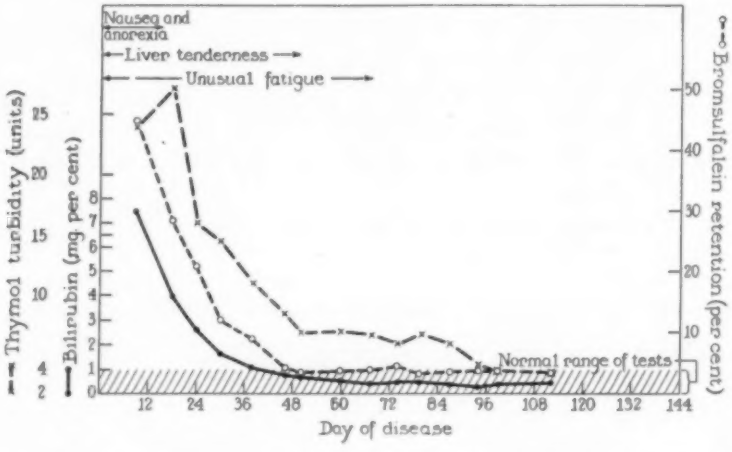

FIG. 1. Serial determinations of plasma bilirubin, bromsulfalein retention and thymol turbidity reaction of the serum in a patient with acute infectious hepatitis showing a normal convalescence.

(2) relapse with transition to chronic hepatitis; (3) chronic hepatitis with persistent bromsulfalein retention; and (4) persistent hyperbilirubinemia, symptomatic and asymptomatic. While such a classification is admittedly artificial, some division was indicated because the patients differed markedly in the type of liver impairment that persisted.

GROUP I: SIMPLE RELAPSE WITH RECOVERY

This was the most common group requiring prolonged hospitalization, accounting for 47 of the 60 cases. Only those patients were included who showed an increase in bromsulfalein retention in more than one determination during convalescence. This was always accompanied by an increased thymol turbidity reaction of the serum and usually by a return of clinical symptoms. Figure 2 shows serial determinations in a typical case. Following the cessation of acute symptoms, the plasma bilirubin concentration and the bromsulfalein retention decreased rapidly, just as in the cases showing

a normal convalescence. The serum thymol turbidity values fell more slowly. Approximately one week after admission, the bilirubin level and the bromsulfalein retention had returned to normal; the patient felt well and was anxious to be discharged. After a period of full activity, this patient then developed marked fatigue and an increase in the size of the liver accompanied by tenderness. The return of these clinical indications of liver insufficiency was immediately reflected in an increase in bromsulfalein retention which remained at an abnormal level for the following 10 weeks. The concentration of plasma bilirubin remained normal during the period of relapse. The thymol turbidity values showed a delayed fall at the end of the original acute attack and leveled off at approximately 14 units. Approximately

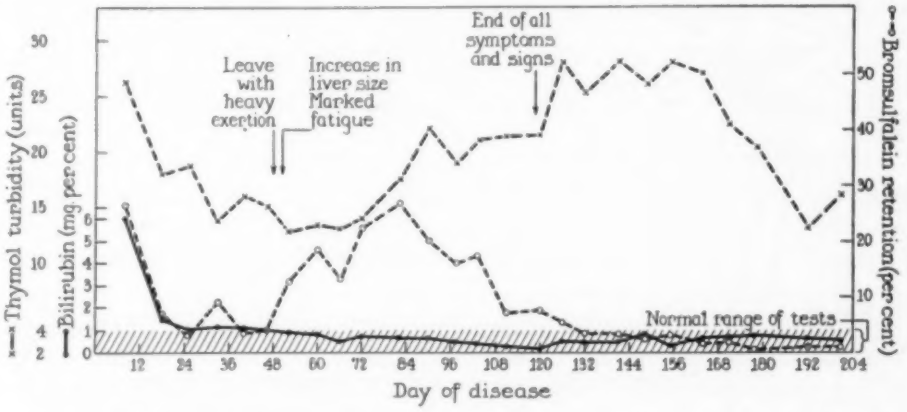

FIG. 2. Serial determinations of plasma bilirubin, bromsulfalein retention, and thymol turbidity reaction of the serum in a patient showing a typical relapse.

three weeks after the onset of the recurrence of symptoms, a definite rise in the values for this test occurred and the elevation persisted for several months.

The other cases in this group were similar to the one discussed above. Tenderness of the liver was the most common physical finding during relapse and was the most useful sign in following the patients clinically. Unusual fatigue, anorexia, pain over the liver, and increase in the size of the liver were frequently encountered. Twenty per cent of the patients in this group showed no clinical signs or symptoms during relapses that were plainly evident through serial determinations of liver function (figure 5).

Measurement of bromsulfalein retention was the most useful single laboratory test for detecting and following both the symptomatic and asymptomatic types of relapse. The results of the test correlated well with the signs and symptoms displayed by each patient, usually showing an increase on the same day that a clinical relapse was noticed. Figure 3 shows graphically the course of a patient who, following a test period of exertion, had an increase in bromsulfalein retention three hours after he developed pain and

tenderness over the liver. This figure also illustrates the value of bromsulfalein retention determinations in the presence of elevated bilirubin levels. Divergence in the usual close parallelism of simultaneous determinations of these two tests gave the first indication of an abnormal convalescence.

Only 35 per cent of these cases in Group I showed a rise in plasma bilirubin levels during relapse. When present, the elevation was very slight (figure 3) and was accompanied by clinical icterus in only one case (figure 4). This test, therefore, was of considerably less value in following relapses than was the determination of bromsulfalein retention.

Results of thymol turbidity measurements reflected every relapse in Group I; the delayed rise and prolonged elevation of values resulting from serial determinations in these cases have been described separately.[11] This test also proved of value in identifying patients that might be candidates for

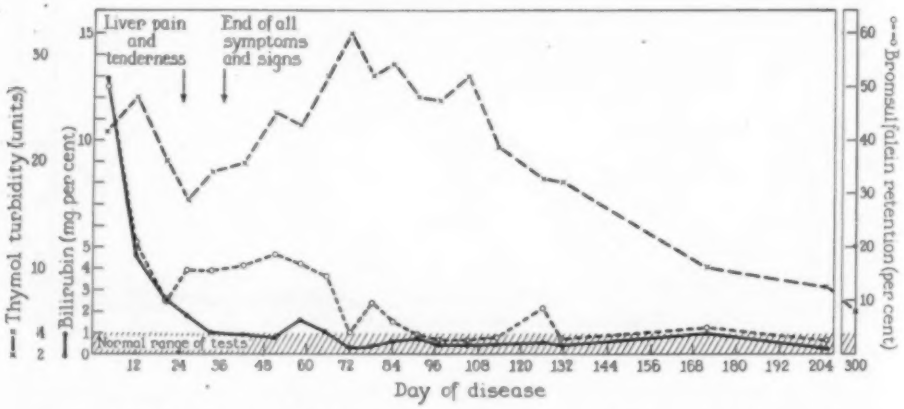

FIG. 3. The detection of a relapse early in convalescence from acute infectious hepatitis. The value of simultaneous serial determinations of plasma bilirubin and bromsulfalein retention in the presence of jaundice is also illustrated.

relapse. In 90 per cent of the cases an elevation above 12 units was found at the time that the relapse began. Such an elevation in a single determination could not be considered significant because of the delayed fall in values for this test in patients showing normal convalescence. However, if such an elevation persisted at a fixed level in several determinations over a period of more than 10 days, the possibility of relapse could be strongly suspected. The patient illustrated in figure 5 showed such a sustained elevation for six weeks prior to relapse.

In one patient of Group I (figure 4) marked clinical symptoms and signs recurred during a relapse precipitated by full activity. Nausea, vomiting, anorexia, abdominal pain, and enlargement and tenderness of the liver were conspicuous clinical features of this recurrence, and the patient was more severely ill than in the initial attack. Bromsulfalein retention and thymol turbidity determinations reached extremely high values. The bilirubin level also rose and the patient developed definite clinical icterus.

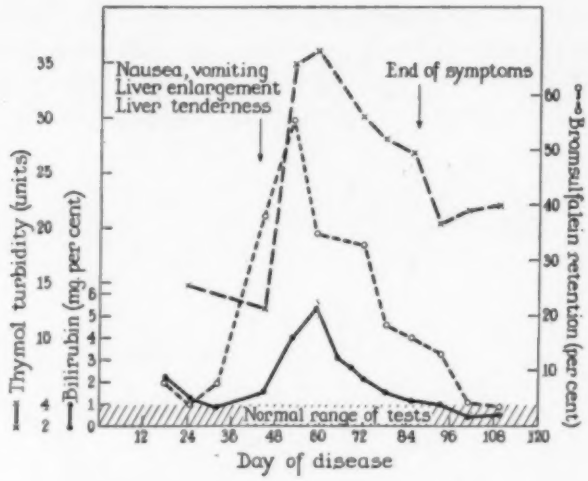

FIG. 4. Severe relapse of acute infectious hepatitis with recurrent icterus.

Exertion has been mentioned as a factor in the precipitation of relapses. Thirty-eight of the 47 cases described above suffered relapses during a test leave period when full activity was resumed for the first time. A typical case is illustrated in figure 2. While on leave, the patient took a long train trip. The following morning he was very tired and unable to eat. These symptoms persisted and, on his return to the hospital three days later, it was found that his bromsulfalein retention had increased. It then remained abnormal for approximately 10 weeks. In nine of the 47 cases no definite inciting factors could be discovered; in fact, two patients developed a relapse while on complete bed rest. One patient (figure 5) was kept in bed, although he felt perfectly well, in order to facilitate the return to normal values of the

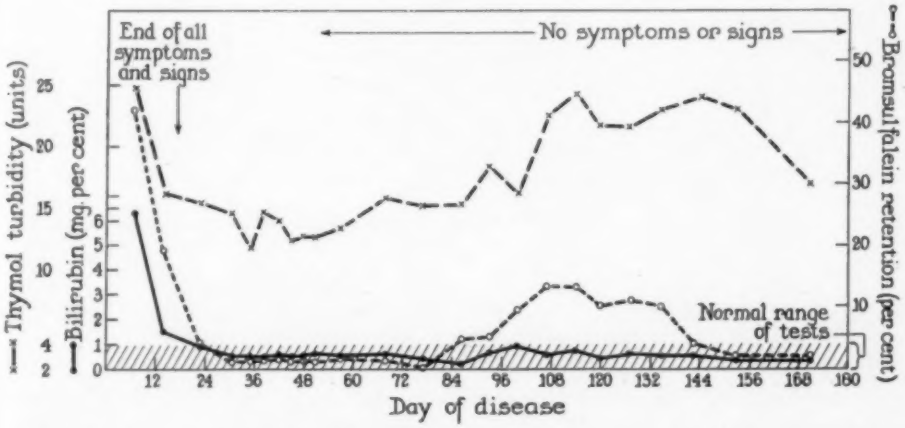

FIG. 5. Asymptomatic relapse late in convalescence from acute infectious hepatitis illustrating (1) relapse during bed rest therapy, (2) the significance of a sustained elevation of the thymol turbidity test during convalescence.

thymol turbidity test. On the eighty-seventh day of his illness he developed a slight increase in bromsulfalein retention and then showed laboratory evidence of a relapse for a six-week period despite continued bed rest. At no time during this period did the patient develop any symptoms or signs of

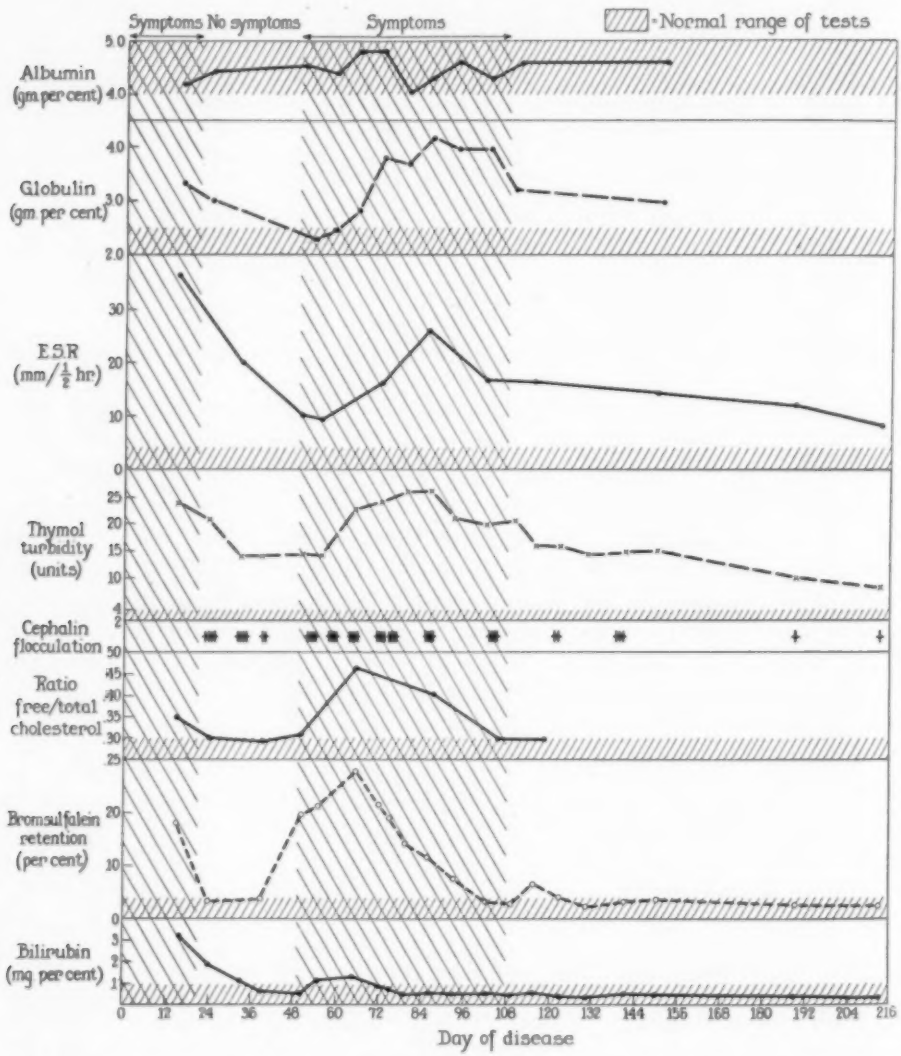

FIG. 6. Serial determinations of multiple tests of liver function in a patient showing a typical relapse of infectious hepatitis.

liver insufficiency. These two cases show definitely that factors other than exertion may be concerned in the development of relapses.

Study of the mild relapses offered an unusual opportunity for comparative evaluation of various liver function tests (figure 6). Results of the plasma

bilirubin level, the bromsulfalein retention test and the thymol turbidity reaction of the serum have been described. Other tests of liver function also reflected the state of relapse. The ratio of free to total cholesterol was found to be a very sensitive test, and serial determinations produced curves closely paralleling those of bromsulfalein retention. This test was not used regularly because of the technical difficulties in making accurate determinations. Serial hippuric acid synthesis measurements were also found to reflect some of the relapses in a manner similar to those of bromsulfalein retention. However, during very mild relapses there was no change, indicating that under these conditions hippuric acid synthesis is not so sensitive a test as is bromsulfalein retention.

The cephalin flocculation test was used in some of the cases (figure 6). The values roughly paralleled those of the thymol turbidity reaction, but, because quantitative measurements were more difficult, serial determinations of the cephalin flocculation test did not produce curves that could be clearly interpreted. The plasma albumin level was altered very little during relapse. However, the total plasma globulin showed a delayed elevation and roughly paralleled the thymol turbidity reaction of the serum. The erythrocyte sedimentation rate, although not a liver function test, showed marked alterations during relapse and serial determinations closely followed the pattern of the globulins. The protein changes following relapse will be described in more detail in a separate communication.

Patients who had transitory elevations in bromsulfalein retention and thymol turbidity values were not included in the group with relapses. However, it must be emphasized that all degrees of reversal may occur during convalescence from infectious hepatitis, ranging from mild asymptomatic changes, through the definite relapse patterns discussed, to the severe relapses that occasionally end in death.[6]

As soon as the onset of a relapse was detected by an increase in bromsulfalein retention, the patient was returned to complete bed rest until the results of this test reached a normal level. All 47 of the patients in the first group showed complete recovery from their relapses and were able to tolerate a second period of full activity without developing further trouble.

Group II: Relapse with Transition to Chronic Hepatitis

Two patients suffered relapses that began in a manner similar to those described in Group I. However, these men did not recover entirely, but showed persistent slight aberrations in bromsulfalein retention and thymol reactivity of the serum for more than 12 months. In addition, both of these patients complained of fatigability and occasional episodes of pain and tenderness over the liver throughout this period. Figure 7 shows the persistent abnormal values of tests of liver function in one of the patients. Somewhat less significance can be applied to the persistent elevation of the thymol turbidity values in these two cases because in other patients showing

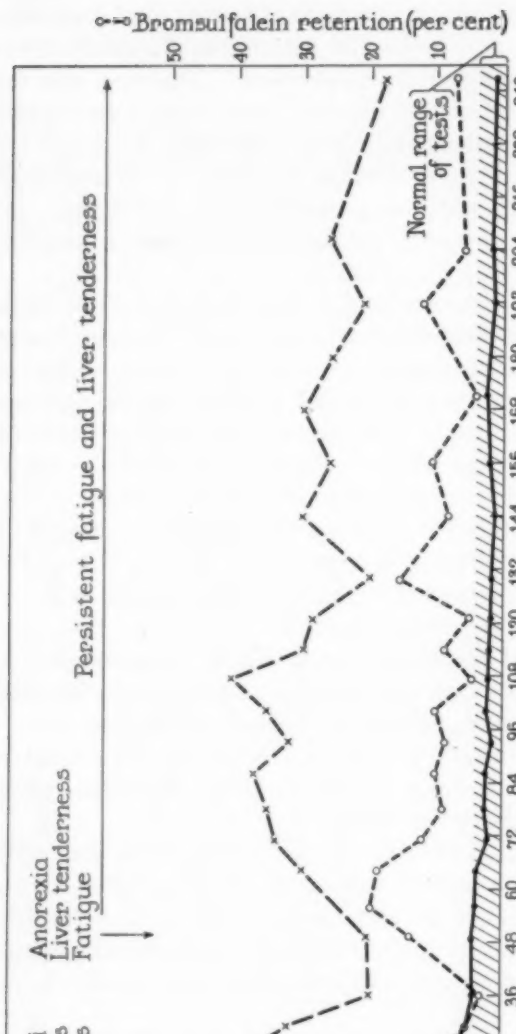

FIG. 7. Serial liver function determinations in a patient showing chronic hepatitis following a relapse.

complete recovery from relapse the values for this test remained elevated for many months. The slight but definite increase in bromsulfalein retention, however, correlated well with persistent symptoms of slight disturbance in the function of the liver. Both of these patients showed a persistent increase in the globulin of the serum, but the albumin level remained normal. No spider angiomata were found. The men are still being followed carefully and appear to be showing slight improvement although fatigability and liver tenderness persist.

Group III: Chronic Hepatitis with Persistent Bromsulfalein Retention

This group included four of the 60 patients showing abnormal convalescence, and was characterized by elevation of bromsulfalein retention with persistent clinical symptoms and signs of disturbance in the liver for more than 12 months. Since these patients showed little evidence of improvement during the usual period of convalescence, they could not be classified with those in the group with relapses. Figure 8 illustrates a typical case. The symptoms of the acute attack in this instance were mild and there followed rapid subsidence of jaundice and gastrointestinal distress. The liver, however, remained slightly enlarged and definitely tender and showed no evidence of improvement during the entire 12 months that the patient was in the hospital. Tenderness of the liver manifested itself in several ways: (1) light palpation of the liver elicited slight pain which often persisted for as long as two days; (2) sleeping on the right side caused local discomfort; (3) pain and tenderness occurred over the left lobe of the liver following large meals to such an extent that the patient hesitated to eat freely. In addition, this patient showed marked fatigue after mild exertion, and was unfit for work. He is still being followed after 18 months and the undue fatigue and tenderness of the liver persist, although there is some improvement in his general condition. Several new crops of spider angiomata developed during the year of observation. There was a persistent marked increase in bromsulfalein retention as shown in figure 8. Values for the thymol turbidity test were only slightly elevated but remained abnormal over the entire period of hospitalization. Slight, but definite, diminution of the albumin of the plasma was also present associated with slight elevation of the globulin, and the A/G ratio averaged 1.1. The cephalin flocculation test never became positive.

The remaining three cases of the group were similar to the one described. They were characterized by persistent liver tenderness, unusual fatigue and increased bromsulfalein retention. The thymol turbidity values were only slightly elevated in two of the cases, while in one they were normal in the presence of severe clinical symptoms. The thymol turbidity test was of little value in following these men and did not give the high values seen in the group of patients with relapses. In all but one of the patients, new spider

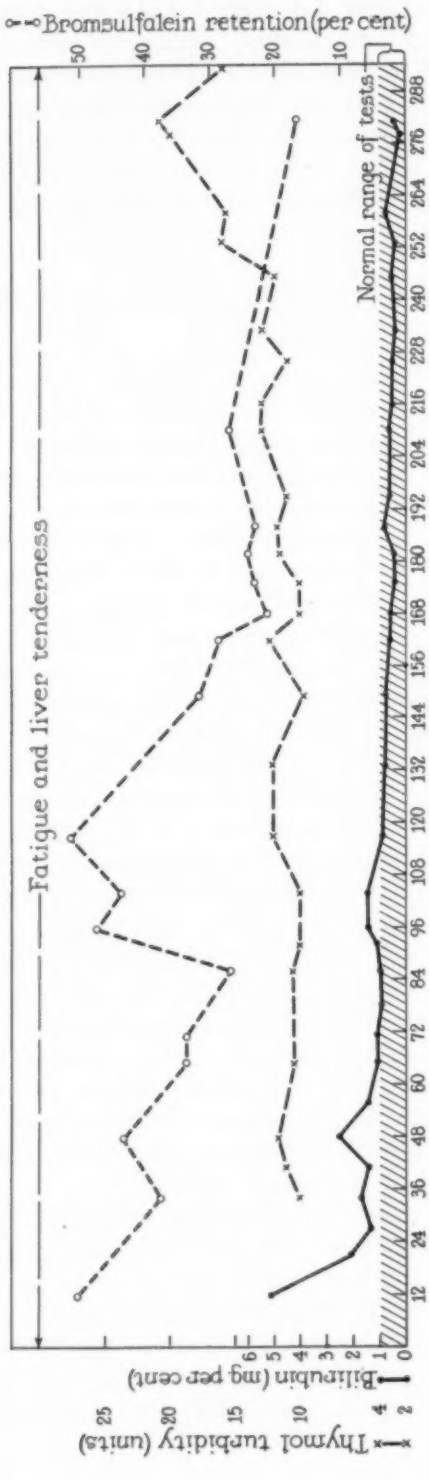

FIG. 8. Serial liver function determinations in a patient showing severe chronic hepatitis following an acute attack of infectious hepatitis.

angiomata developed more than six months after the acute attack of infectious hepatitis. The four patients in this group showed the most marked symptoms and signs of persisting liver insufficiency of the entire series. These findings correlated well with the increased bromsulfalein retention which was also more marked than in any other group.

Group IV: Persistent Hyperbilirubinemia

Seven of the 60 patients showing an abnormal convalescence required prolonged hospitalization because of persistent elevation of plasma bilirubin values and were finally discharged despite an elevation above 1 mg. per cent. Figure 9 illustrates a typical case from this group. The acute phase of

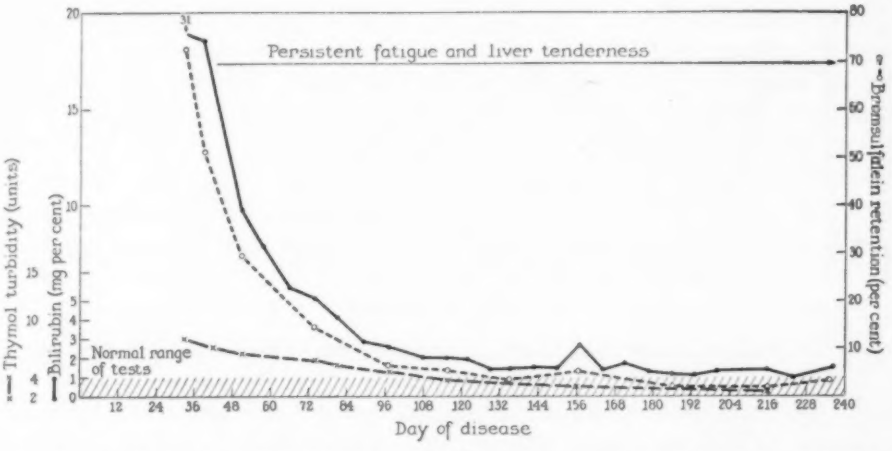

Fig. 9. Persistent hyperbilirubinemia following an acute attack of infectious hepatitis.

hepatitis in this patient was severe and was characterized by extremely high plasma bilirubin values. These values fell to normal more slowly than in the average uncomplicated case, finally leveling off at approximately 2 mg. per cent, despite the fact that the patient was kept at complete bed rest for three months. Hyperbilirubinemia persisted throughout the 200 days that the patient was in the hospital. The bromsulfalein retention and thymol turbidity determinations gave no indication of an abnormal convalescence. The cephalin flocculation test became negative at the end of the acute attack. In addition to the elevation in plasma bilirubin, this patient showed persistent fatigue throughout the period of observation. At the time of discharge he was unable to walk more than two blocks without feeling exhausted. The only other finding that was noted was an occasional episode of slight tenderness of the liver. Five other patients showed a similar course and were discharged after a long period of hospitalization with bilirubin values above 1 mg. per cent. They differed only in that the clinical picture initially was considerably milder with less intense icterus. The bromsulfalein retention

and the thymol turbidity tests gave no indication of an abnormal course. In these men the excretion of bilirubin by the liver appeared to be selectively impaired.

The seventh case in this group (figure 10), in addition to showing persistent hyperbilirubinemia, suffered a relapse during convalescence, characterized by transitory mild symptoms and a rise in bromsulfalein retention and thymol turbidity values. Throughout the entire course of this patient's

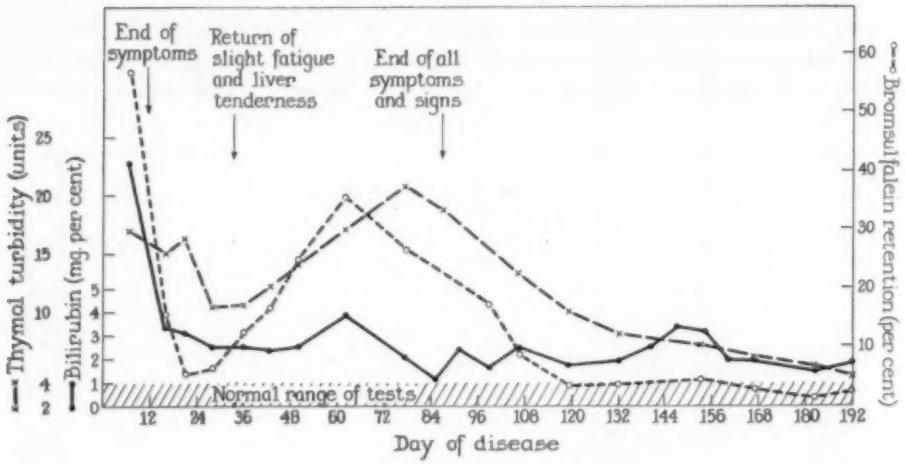

FIG. 10. Relapse during acute infectious hepatitis with persistent hyperbilirubinemia.

illness the bilirubin level stayed at approximately 3 mg. per cent. The mild symptoms during the relapse disappeared and the patient was discharged with an asymptomatic hyperbilirubinemia after being hospitalized for 186 days. This case suggests some relationship between this group and Group I. The persistent elevation of the plasma bilirubin in Group IV was mainly in the indirect-reacting component, while the 1-minute or direct-reacting portion fell to normal at the end of the acute attack (table 1). It is of significance

TABLE I

Relative Amounts of the Direct and Indirect Bilirubin Components at Various Periods during the Illness of the Patient Illustrated in Figure 9

Day of Illness	1 Min. or Direct Reacting Bilirubin mg.%	30 Min. or Total Bilirubin mg.%	Indirect Reacting Bilirubin % of total
34th	14	31	55
58th	4.1	8.0	49
80th	1.9	4.0	52
120th	1.1	2.5	56
135th	0.1	1.5	93
172th	0.2	1.8	89
200th	0.1	1.3	92
236th	0.1	1.6	94

that the slight persistent elevation of the plasma bilirubin was associated with symptoms of liver insufficiency in three of the seven cases.

Discussion

Relapse was by far the most common cause of prolonged hospitalization in the group of 60 patients discussed. This usually occurred following the first period of full activity. Many other patients, not included in the group, were found to develop transitory changes in liver function tests following such activity. It was evident that most patients with infectious hepatitis were very susceptible to further injury of the liver during the convalescent period despite the fact that they no longer showed clinical signs or symptoms of the disease and had normal values for plasma bilirubin and bromsulfalein retention. It is undoubtedly important that these patients be followed carefully with tests of liver function during the period of resumption of their activity. Occasionally, it was possible to anticipate relapse because of sustained elevation of the thymol turbidity test at a fixed level during convalescence. However, the value of this test in predicting relapses was somewhat lessened by the fact that at times it fell to normal slowly even in patients who showed a normal convalescence.

In the average case, symptoms and signs of liver insufficiency were very mild during relapse; 20 per cent, or 10, of the 49 cases in Group I showed no clinical signs or symptoms. Clinical jaundice was present in only one case and plasma bilirubin elevation was detected in only one third of the patients. Most of the relapses, therefore, might have gone undetected. It was only by means of serial determinations of bromsulfalein retention that they were clearly recognized. Relapses have been described in infectious hepatitis which were usually apparent only because of a return of jaundice and clinical signs and symptoms of the disease. The importance of the bromsulfalein test in detecting the relapses that occur without jaundice has not been sufficiently emphasized. This test became positive almost immediately after the onset of a relapse and, as a result, these patients could be returned immediately to bed rest.

The importance of bed rest in preventing chronic liver disease has never been clearly established. However, since activity was the usual initiator of a relapse, it is reasonable to believe that limitation of activity might be of considerable importance after the relapse has begun. Fishman [6] described fatal relapses in two men which occurred under combat conditions. These relapses corresponded in time to those in Group I of the present study. The severity of the relapses may very well have resulted from the fact that the two men were forced to continue activity until marked jaundice appeared. Two ex-service men, who are now being studied at this hospital, present the clinical picture of severe cirrhosis of the liver following attacks of infectious hepatitis four years ago. Both men developed relapses with return of jaundice approximately two months after the initial attack. They continued

activity despite these changes because of wartime duties. The jaundice that returned during the relapse states never disappeared and both patients have gradually failed. In the present series, all but two of the 49 patients who suffered relapses recovered entirely in less than six months' time. It seems possible that the early detection of the relapses and immediate restriction of activity may have been partially responsible for the subsequent benign course in the majority of the patients.

The question as to whether the relapses were caused by a reactivation of the virus of infectious hepatitis has not been answered. Neefe [27] attempted to transmit the disease to human volunteers by means of material obtained from patients with a lingering hepatitis during a period that corresponded to the time of the relapses described in the present paper. The results were not conclusive. Further work is necessary to elucidate this important question.

In addition to those showing relapses, four patients (Group III) were described who showed marked symptoms of fatigue and liver tenderness continually for more than 12 months. These patients apparently never recovered completely from their initial attack. Bromsulfalein retention remained at a high level throughout the period of observation. The possibility of the development of cirrhosis must be considered in these cases. Two of these patients now show alteration of A/G ratio by virtue of a fall in albumin and elevation of globulin, but there is no evidence of edema or ascites. Several new crops of spider angiomata have appeared in three patients of the group. The prognosis is undoubtedly more grave in these patients who showed continued bromsulfalein retention for more than 12 months than in those in Group I who showed bromsulfalein retention solely during the course of a relapse, even though the values may have reached higher levels in the latter group.

The fourth group of patients, seven in number, showing an abnormal convalescence, was characterized by a selective abnormality in bilirubin metabolism. All other tests of liver function were consistently negative. These included determinations of urine bilirubin, bromsulfalein retention, the thymol turbidity reaction, the thymol flocculation reaction,[10] the cephalin flocculation reaction, the ratio of free to total cholesterol, and the plasma proteins. Three of the patients had persistent symptoms of fatigue and tenderness of the liver associated with elevated plasma bilirubin for more than 12 months after the initial attack. The remaining patients were without symptoms despite persistent mild hyperbilirubinemia. The elevation in plasma bilirubin in all the patients was usually entirely of the indirect reacting type. They presented the picture of a hemolytic jaundice without other evidences of red blood cell destruction such as anemia, increased fragility of the red cells and splenomegaly. This group is definitely different from the other cases discussed.

As has been pointed out, liver function tests often showed evidence of an

abnormal convalescence in the absence of other findings. However, it should be emphasized that in all cases in which there were clinical symptoms and signs of relapse or of a lingering hepatitis, there were also accompanying aberrations in at least one of the three main liver function tests mentioned.

The eventual outcome of the 60 patients in the four groups showing abnormal convalescence is uncertain. At present, it can be stated that all but eight recovered sufficiently in less than one year to tolerate a test period of full activity without symptoms or signs of liver insufficiency. The eight who did not recover in this manner are still being observed carefully. The factors responsible for such a prolonged course are not clear. The severity of the initial attack had no relation to the incidence of relapse or prolonged convalescence. Four of the eight had comparatively mild acute attacks of infectious hepatitis. The only tangible factor was age. The eight patients referred to above averaged 31 years of age, while the average age of the entire group of 350 patients was 24. This may be an important difference in determining ability to recover and, in light of these data, it is undoubtedly wise to manage patients over 30 years of age with acute infectious hepatitis more conservatively than those in younger groups.

This study has dealt only with those patients showing abnormal convalescence. The other members of the group of 350 patients who showed a normal convalescence and who were able to tolerate a test period of full activity without difficulty should also be observed for development of signs of hepatic insufficiency at some future time. Studies on the entire group of patients must be continued for many years in order to answer the question of the development of cirrhosis. The patients who experienced the early complications described in this paper should be observed with special care.

Summary

1. Three hundred and fifty patients with acute infectious hepatitis were studied.

2. Sixty, or 17 per cent, showed abnormal convalescence.

3. Of the 60, 47 showed a simple relapse with recovery; two, relapse with transition to chronic hepatitis; four, chronic hepatitis with persistent bromsulfalein retention; and seven, persistent hyperbilirubinemia.

4. A comparative evaluation of certain liver function tests used in following the patients with abnormal convalescence was made.

5. Determination of bromsulfalein retention was found to be of particular value in detecting relapses.

6. The importance of the combined use of the plasma bilirubin level, the bromsulfalein retention and the thymol turbidity reaction of the serum for following the various types of persistent impairment of the liver, was emphasized.

7. Eight patients, or 2.3 per cent, did not recover completely after more than one year's time.

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ARTERIALIZATION OF INTERNAL JUGULAR BLOOD DURING HYPERVENTILATION AS AN AID IN THE DIAGNOSIS OF INTRACRANIAL VASCULAR TUMORS *

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The diagnosis of intracranial vascular tumors is important because treatment is, as a rule, nonsurgical; often roentgenological treatment is the procedure of choice. In the diagnosis of vascular tumors certain criteria have been useful: (*a*) Roentgenologic evidence of calcification of the vessel walls; (*b*) Roentgenologic evidence of a vascular pattern from erosion of the inner table of the skull; (*c*) Pneumoencephalographic evidence of a space-consuming lesion as indicated by depression of the ventricle with, however, an apparent increase in the depth of the subarachnoid spaces over the convexity; (*d*) The presence of a bruit; (*e*) The presence of angiomata in the fundi (i.e., with cerebellar hemangioma of the Lindau type) or of angiomata in the pancreas and kidneys; (*f*) The presence of morphological changes in the cerebral vessels as demonstrated by intracranial angiography. Diagnosis, however, is still a very difficult problem, and the addition of any further diagnostic procedures would be helpful in avoiding unnecessary operations.

In the course of study of 69 samples of internal jugular blood taken before and during hyperventilation in persons without vascular tumors, it was found that the usual reaction was for the oxygen content to fall during hyperventilation. In a small percentage of the cases the oxygen content remained unchanged or rose slightly. Evidence is available that during hyperventilation cerebral blood flow decreases while extracranial blood flow to the head usually increases, and the composition of the internal jugular blood reflects, in part, the cerebral vasoconstriction plus contributions from extracranial sources through cranial anastomoses.[1]

The presence of a vascular tumor might result in shunting of blood through the vascular anomaly during the cerebral vasoconstriction associated with hyperventilation, hence leading to increased arterialization of the internal jugular blood. If this shunt were of any size, this would be revealed by rising O_2 and falling CO_2 contents of the jugular blood, in contrast to the usual response. Opportunity to test this point presented itself when a patient with a proved intracranial vascular tumor was studied. The vascular character of the tumor in this case was not diagnosed preoperatively. Of the above criteria, only the pneumoencephalographic findings of depression

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of a lateral ventricle were present preoperatively and this suggested merely the presence of a space-consuming lesion.

Case Report

The patient was a 22 year old single white man with a four and one-half year history of attacks characterized by right-sided numbness beginning in the tips of the fingers and progressing to the hand, arm, right half of the face and tongue, then to the right half of the chest and abdomen and finally, to the right leg and foot. This was followed by right hemiparesis, which in the earlier attacks lasted about 24 hours,

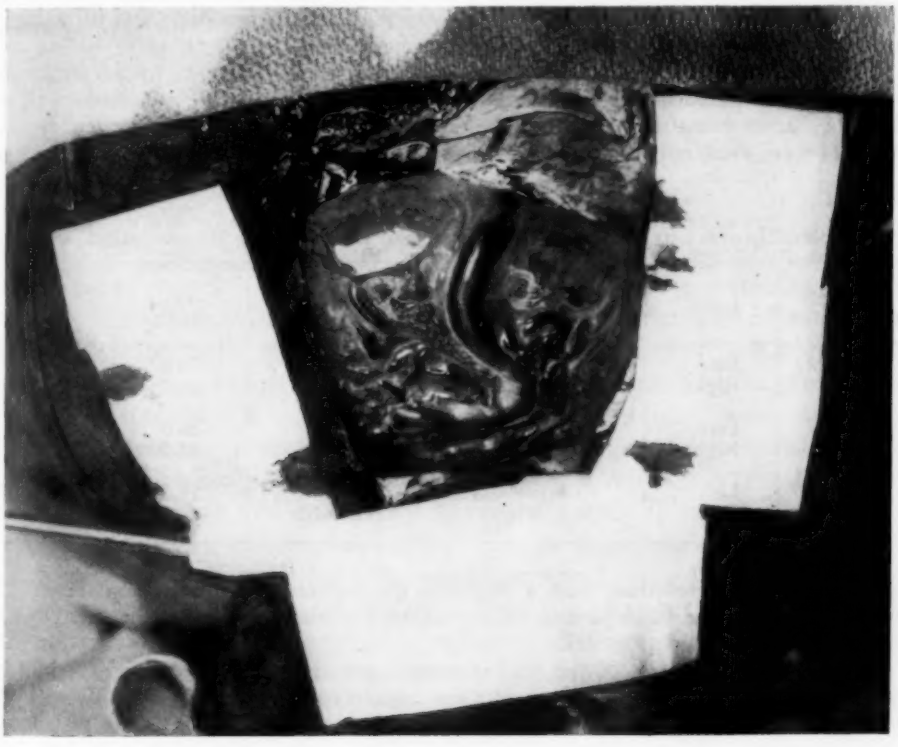

Fig. 1. Photograph of hemangioma taken at time of operation.

but in the last few months had become permanent. These attacks occurred two to three times a week. Significant physical findings were weakness of the right lower face and right extremities with some clumsiness of the fingers and toes in performing fine movements and some spasticity of the right leg when walking. There was slight drift of the extended right arm. No bruit was heard on auscultation of the head.

Pneumoencephalogram revealed some depression of the roof of the left lateral ventricle in portions three and four and the first part of six. The subarachnoid spaces showed slightly decreased filling in the parietal regions bilaterally.

A left parietal osteoplastic craniotomy was performed exposing a wide-spread vascular malformation in the left frontoparietal region, the extent of which is evident in the accompanying photograph (figure 1). Included in this was a large main

vessel 3 to 4 mm. in diameter with occasional tributaries, and several accessory vessels of smaller size. A deep groove was found in the bone overlying the large vessel. (In retrospect this groove was evident in the roentgenogram.) The blood in all of the major vessels of the tumor seemed arterial in appearance. Neither compression of the large vessel above described, nor compression of each of the main vessels of the neck seemed to alter blood flow through the tumor. No thrill or bruit was elicited at this time, but one week postoperatively a loud bruit was heard for the first time over the entire head, loudest on the left.

Bilateral Internal Jugular Vein Puncture. Bilateral internal jugular vein puncture was carried out six months post-operatively. After procaine infiltration of the overlying skin and subcutaneous tissues, the internal jugular veins were punctured as close to their point of emergence from the jugular foramen as possible by inserting the needle between the mastoid process and the angle of the mandible and directing it upward.[2] Blood samples were obtained simultaneously from both veins before and again at one and three minute intervals after beginning vigorous hyperventilation. Indwelling obturated needles were used. The blood samples were collected in tight-fitting syringes containing 1 to 2 c.c. of mineral oil, and stored in mercury vessels. Samples were analyzed for oxygen and carbon dioxide by the Van Slyke manometric

TABLE I

Simultaneous Left and Right Internal Jugular Blood During Hyperventilation

Time of Hyperventilation	Sample	Whole Blood Oxygen Vol. %	Oxygen Saturation %	Whole Blood CO_2 Vol. %	pCO_2 mm.Hg	pH
Control	Left	17.2	79	53.5	50.0	7.34
	Right	18.8	86	52.5	48.0	7.35
1'15"	Left	19.1	87	41.8	26.0	7.55
	Right	19.8	91	41.2	25.0	7.57
3'15"	Left	19.3	90	42.0	25.5	7.59
	Right	20.5	95	41.3	24.5	7.60

technic; pH was determined with a MacInnis glass electrode. From the data on pH, carbon dioxide content and hematocrit the carbon dioxide tension was calculated by the Henderson-Hasselbalch formula.

Results. The results of the studies carried out are listed in table 1. It will be noted that the prehyperventilation values for oxygen content and saturation were high, and that during hyperventilation these values approached those of arterial blood (saturation 90 to 95 per cent). The carbon dioxide content fell from 53.5 to 42.0 volumes per cent on the left and from 52.5 to 41.3 volumes per cent on the right. The pH rose from 7.34 to 7.59.

DISCUSSION

The notable finding is the marked rise in oxygen content and oxygen saturation of the internal jugular blood during hyperventilation so that it closely approaches the composition of arterial blood. The changes in carbon dioxide content and pH are consistent but less striking, so that for diagnostic purposes determination of oxygen saturation alone gives the necessary information. The results may be compared with analyses of 69 internal jugular blood specimens from normal medical students and coöperative

patients who had no cerebral vascular tumors.[1] There were no instances among this group in which a comparable rise in oxygen saturation during hyperventilation was noted. In 60 of the 69 analyses the oxygen saturation fell to a mean average of 37 per cent (range 14 to 58 per cent). We have designated this pattern I.[1] In 9 of the 69 analyses the oxygen saturation remained unchanged or rose slightly (average, 65 per cent, range 50 to 76 per cent). We have designated this pattern II. Evidence has been presented that pattern II represents examples of internal jugular blood to which a high proportion of extracranial blood has been added.[1] In this relatively large experience we have never encountered in other subjects an oxygen saturation during hyperventilation as high as that noted in our patient with the intracerebral vascular tumor. Even the oxygen saturation of external jugular blood during hyperventilation in two patients (values of 77 per cent and 87 per cent respectively) did not exceed that noted in our patient. This would suggest that during hyperventilation there is greatly increased shunting of blood through the vascular tumor.

The prehyperventilation oxygen saturations in our patient were also high (79 to 86 per cent). In the control subjects the prehyperventilation oxygen saturations averaged 56 per cent with a range of 34 to 69 per cent in the 60 examples of pattern I, and averaged 63 per cent with a range of 51 to 74 per cent in the 9 examples of pattern II. As compared to control subjects the prehyperventilation values in the patient are suggestive of the diagnosis but not as decisive as the values during hyperventilation. Occasionally in patients with severe encephalopathy and coma comparatively high venous oxygen saturation may be noted in the presence of reduced cerebral metabolism. Thus among 18 patients with encephalopathy from various causes one was found with an internal jugular oxygen saturation of 84 per cent. This patient had malignant hypertension and uremia and was in coma at the time of the examination.[3] Obviously diffuse encephalopathy is not apt to present an important problem in the differential diagnosis of intracerebral vascular tumors except perhaps in instances in which such tumors have recently been complicated by intracerebral or subarachnoid bleeding.

Internal jugular punctures cannot be expected to be of help in locating the tumor because of the many anatomic variations in the great venous sinuses.[4] Although the vascular anomaly in our patient was on the left the oxygen saturation was higher on the right suggesting that a greater proportion of the venous drainage of this tumor was directed toward the right lateral sinus. Anatomically it is conceivable that in some cases the venous drainage of the tumor would be to one side, not necessarily the same side. Hence, the finding of normal blood on one side does not rule out vascular tumor. For ordinary purposes, then, it is probably best to study blood from the internal jugular vein on one side and if this is normal or equivocal, to examine the opposite side.

Technically the procedure is simple and without risk. It is much less formidable than the injection of opaque materials into the internal carotid

artery. In many hundred internal jugular vein punctures performed by us in the past six years we have never encountered any serious accident. Occasionally a facial weakness lasting a few hours results from infiltration of procaine in the region of the tip of the mastoid and twice in our experience the facial weakness lasted several weeks, probably due to direct trauma to the facial nerve by the needle.

Conclusions

1. In a patient with a demonstrated intracerebral vascular tumor in the left fronto-parietal region, hyperventilation increased the oxygen saturation of the internal jugular blood to almost arterial levels (95 per cent). This was never observed in 69 examinations of internal jugular blood of individuals without vascular tumors.

2. This procedure is suggested as an aid in the diagnosis of vascular intracranial tumors and in the evaluation of therapy.

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PENICILLIN IN THE TREATMENT OF EARLY SYPHILIS, 429 PATIENTS TREATED WITH 1,200,000 UNITS IN 90 HOURS*

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THE problem of time-dose relationship in the treatment of early syphilis has been foremost in the investigation of this mode of therapy. It has been established that doses of less than 1.2 million units of penicillin were inadequate as measured by the relapse rate.[1, 2]

The use of a total dose of 1.2 million units of penicillin administered over different time periods, and the combination of this amount with artificial fever therapy (hypertherm) was delegated to this Center by the National Research Council.

The present report concerns only the group of patients treated by the following schedule: each patient received 40,000 Oxford units of sodium penicillin intramuscularly every three hours for 30 doses, over a period of three and three-quarter days (1.2 million units total). The results of treatment by the other schedules will form the basis of subsequent reports.

TABLE I

Distribution by Sex and Race

Race	Total	Sex	
		Male	Female
Total	429	249*	180
Negro	362	202	160
White	66	46	20

* Total figure includes one American Indian.

A total of 429 patients were treated by this schedule between July 19 and November 30, 1944. All patients exhibited darkfield positive lesions of primary or secondary syphilis prior to treatment. No further treatment was given unless either clinical or serologic relapse or pregnancy occurred.

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From the Chicago Intensive Treatment Center, Venereal Disease Control Program, Chicago Board of Health in coöperation with the United States Public Health Service.

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The patients' ages ranged from four to 56 years; 74 per cent were 25 or under; 87.9 per cent were 30 or under. The distribution of patients according to sex and race is presented in table 1. The distribution according to stage of syphilis at the time of treatment is listed in table 2.

TABLE II

Distribution of Stage of Syphilis

	Number		Per Cent
Total Diagnoses	429		100.0
Primary Syphilis	151		32.5
Seronegative		47	11.0
Seropositive		104	24.2
Early Secondary Syphilis	216		50.3
Relapse from Prev. RX	62		14.5
Relapsing Secondary		53	12.4
Monorecidive		5	1.1
Serologic		2	0.5
Neurorecurrence		1	0.25
Arseno-bismuth Resistant		1	0.25

Sixty-two of the 429 patients had received previous treatment for syphilis. This group included patients who had exhibited clinical and/or laboratory evidence of relapse after varying amounts of arsenic and bismuth, penicillin and arsenic, or penicillin alone. The remaining 367 patients had never been previously treated for syphilis.

For comparative purposes, the status of all patients and a separation of the results according to diagnosis at three-, six-, nine-, twelve- and fifteen-month intervals, after the completion of therapy, are recorded in table 3.

In 90 of the 222 patients included in "status unknown" in table 3, observation was terminated for the following reasons: 16 inducted into the armed forces; eight committed to jail; two died (cause unknown); 10 retreated because of pregnancy, and 54 transferred to other clinics, having moved out of our jurisdiction. One hundred and two of the 222 patients were seronegative at the time of the last examination, before being lost to observation.

COMMENT

There were no patients whose syphilitic lesions failed to heal with this schedule of therapy. Previous experience[2, 3] had shown that surface spirochetes disappeared with lesser amounts of penicillin than were being employed in this series; consequently, darkfield examinations were not done routinely after treatment was instituted.

Three hundred and eighty-two of the patients had been seropositive before treatment. Two hundred and thirty (60.5 per cent) achieved seronegativity after treatment. The number and per cent of patients in each stage of syphilis and the average number of days required to reach sero-

TABLE III

Number and Per Cent of Patients with Early Syphilis Treated with Penicillin from July 1, 1944 Through October 1, 1945, by Diagnosis and Treatment Results at Three Month Intervals

Diagnosis and Observation Period (Months)	Total		Failures					Clinically Negative					
			Total		Serologic	Clinical	Probable Reinfection	Seropositive		Seronegative		Status Unknown	
	No.	%	No.	%				No.	%	No.	%	No.	%
Total:													
3	429	100.0	11	2.5	1	10	—	141	32.9	150	35.0	127	29.6
6	429	100.0	42	9.8	8	33	1	62	14.4	194	45.2	131	30.6
9	429	100.0	54	12.6	11	42	1	38	8.8	182	42.4	155	36.2
12	429	100.0	72	16.8	18	53	1	21	4.9	176	41.0	160	37.3
15	429	100.0	85	19.8	24	56	5	8	1.9	114	26.5	222	51.8
Primary Seronegative:													
3	47	100.0	3	6.4	1	2	—	—	—	31	66.0	13	27.6
6	47	100.0	6	12.8	1	5	—	—	—	27	57.4	14	29.8
9	47	100.0	6	12.8	1	5	—	—	—	22	48.8	19	40.4
12	47	100.0	7	14.8	1	6	—	—	—	20	42.6	20	42.6
15	47	100.0	9	19.2	1	6	2	—	—	9	19.2	29	61.6
Primary Seropositive:													
3	104	100.0	5	4.8	—	5	—	11	10.6	51	49.0	37	35.6
6	104	100.0	11	10.6	1	10	—	5	4.8	59	56.7	29	27.9
9	104	100.0	12	11.6	1	11	—	2	1.9	53	51.0	37	35.5
12	104	100.0	15	14.5	2	13	—	1	1.0	51	49.0	37	35.5
15	104	100.0	18	17.3	4[a]	14	—	—	—	33	31.7	53	51.0
Early Secondary:													
3	216	100.0	3	1.4	—	3	—	98	45.4	63	29.1	52	24.1
6	216	100.0	18	8.4	4	13	1	36	16.6	98	45.4	64	29.6
9	216	100.0	25	11.6	6	18	1	25	11.6	94	43.5	72	33.3
12	216	100.0	35	16.2	9	25	1	13	6.5	91	42.1	77	35.6
15	216	100.0	41	19.0	11	27	3	5	2.3	64	29.6	106	49.1
Previously Treated:													
3	62	100.0	—	—	—	—	—	32	51.6	5	8.1	25	40.3
6	62	100.0	7	11.3	2[a]	5	—	21	33.9	10	16.1	24	38.7
9	62	100.0	11	17.7	3	8	—	11	17.7	13	21.0	27	43.6
12	62	100.0	15	24.2	6	9	—	7	11.3	14	22.6	26	41.9
15	62	100.0	17	27.4	8	9	—	3	4.8	8	12.9	34	54.9

[a] Includes one neurorecurrence.

negativity are presented in table 4. It is recognized that the periods of time reported are crude estimates, inasmuch as it was impossible to determine the exact day that any patient became seronegative.

All but 10 patients received a lumbar puncture before treatment was instituted. Five patients revealed abnormal cerebrospinal fluids, two of whom were neurorecurrences following previous treatment with 600,000 units of

TABLE IV

Number and Per Cent of Seropositive Cases Reaching Seronegativity, by Diagnosis, and the Average Number of Days Before Seronegativity Was Attained

Diagnosis	Seropositive	Seropositive Reaching Seronegativity		Average Number of Days Before Seronegativity Was Attained
		Number	Per Cent	
Total Patients	382	230	60.2	136.7
Primary Syphilis	104	76	73.1	91.7
Early Secondary	216	136	63.0	152.1
Relapsing Secondary	53	14	26.4	199.0
Monorecidive	5	3	60.0	183.0
Serologic Relapse	2	1	50.0	358.0
Neurorecurrence	1	—	—	—
Arseno-bismuth Resist.	1	—	—	—

penicillin in three and three-quarters days. Their spinal fluid findings follow:

Patient	Date	Kahn Units	Lymphocytes	Globulin	Total Protein Mg.%	Colloidal Gold
T. S.	11/ 4/44	4	250	3+	55	1232000000
	5/23/45	4	60	1+	33	2332100000
	Deceased					
V. H.	9/26/44	0	42	2+	40	————
P. E.	10/26/44	20	50	3+	62	5554210000
L. S.	8/25/44	20	2	1+	58	1233210000
	Lost to follow-up					
B. G.	11/20/44	4	4	1+	40	2222210000
	12/ 2/44	0	2	1+	36	————
	3/10/45	0	2	1+	35	————

Eighty-five patients (19.8 per cent of the total patients treated) were known to be treatment failures at the end of 15 months' observation. These consisted of 38 relapsing secondaries; 14 primary syphilis progressing to secondary syphilis; 13 serologic relapses; eight seroresistant * after one year's observation; five relapsing primaries (monorecidive), and two neurorecurrences. Five patients were considered possible reinfections. Case histories of these patients follow:

M. L., male negro, age 20, diagnosed papular and annular secondary syphilis with eroded penile papules, Kahn titer 80 units on August 25, 1944. Received 1.2 million units of penicillin from August 26 to 29, 1944. The lesions healed promptly and 75 days after treatment the patient was seronegative. At this time he was re-admitted with the diagnosis of sulfonamide resistant gonorrheal urethritis, for which he received 150,000 units of penicillin. He remained seronegative through February,

* Any patient with a Kahn titer of 4 units or more at the end of 12 months' observation was declared seroresistant.

1945 (186 days after treatment), at which time he presented himself with a solitary infiltrated darkfield positive penile lesion. Multiple exposures were admitted and three bouts of gonorrhea gave eloquent testimony of these exposures.

R. T., female negro, age 21, diagnosed seronegative primary syphilis on September 13, 1944. Received 1.2 million units of penicillin from September 14 to 17, 1944. The lesion healed and she remained seronegative for 257 days. She was then lost to observation until December, 1945 (470 days after treatment), at which time she presented herself with darkfield positive condylomata lata of the vulva and a Kahn titer of 80 units. The patient's husband had been admitted to this hospital a short time before with darkfield positive primary syphilis.

M. P., male negro, age 40, diagnosed secondary syphilis, eroded penile papules, Kahn titer 20 units on August 1, 1944. Received 1.2 million units of penicillin from August 2 to 5, 1944. The lesions healed and the patient was inducted into the army one month later. He stated that all serologic tests for syphilis had been negative while in the army and that he received no antisyphilitic therapy. He again came under our observation in March, 1945 (233 days after treatment), at which time clinical and serologic examination revealed no abnormalities. He remained seronegative through August, 1945 (373 days after therapy), but presented himself in September (411 days after treatment) with multiple indurated darkfield positive lesions of the penis, Kahn titer 40 units. Numerous exposures were admitted.

R. C., male negro, age 18, diagnosed seronegative primary syphilis, multiple penile chancres on August 21, 1944. Received 1.2 million units of penicillin from August 22 to 25, 1944. The lesions healed and he remained seronegative through May, 1945 (283 days after treatment). On July 9, 1945 (323 days after treatment), he was readmitted with a single, indurated, darkfield positive penile lesion, Kahn titer 40 units. Multiple exposures were admitted.

A. G., female negro, age 27, diagnosed seronegative primary syphilis, chancre at fourchette, on September 18, 1944. Received 1.2 million units of penicillin from September 19 to 22, 1944. The lesion healed and she remained seronegative through September, 1945 (373 days after treatment). In January, 1946 (465 days after treatment), a Kahn titer of 40 units was found, and she was clinically negative. On her next examination (496 days after treatment) a darkfield positive chancre of the right labium majus and papular secondary syphilis were present. Gonorrheal urethritis and cervicitis were proved by bacteriologic studies. Numerous exposures were admitted.

It is interesting to note that this schedule of treatment is considerably more effective than either smaller amounts of penicillin plus arsenic, or half as much penicillin over twice the length of time.[4] Thus, in a study to be published [2] in which 339 patients were treated with 600,000 units of penicillin administered intramuscularly, 10,000 units per injection, at three hour intervals over a period of seven and one-half days, there were 97 failures, or a failure rate of 28.6 per cent. Again, in a study to be published [5] in a series of 107 patients receiving a combination form of treatment of 320 mg. mapharsen administered intravenously, 40 mg. daily, plus 300,000 units of penicillin intramuscularly, 5,000 units per injection, every three hours over a period of seven and one-half days, there were 34 failures or a 31.8 per cent failure rate. For the present, the administration of 1.2 million units of penicillin over a 90 hour period also promises to compare favorably with the same amount of penicillin administered over seven and one-half days.

Reactions during treatment consisted of mild pruritus, systemic and focal Herxheimer reactions, and temperature elevations, none of which necessitated termination of treatment. The temperature elevation was described as primary fever if it occurred during the first 48 hours, and secondary fever, if it occurred three days or more after the initiation of treatment. It is interesting that 25.4 per cent of the patients developed a Grade I secondary fever while being treated with penicillin alone (table 5).

TABLE V

Number and Per Cent of Patients with Reactions

Reactions	Number	Per cent
Total patients treated	429	100.0
Primary fever	241	56.2
Grade I	132	30.8
Grade II	75	17.5
Grade III	34	7.9
Secondary fever	118	27.5
Grade I	109	25.4
Grade II	9	2.1
No reactions	70	16.3

Definitions:
Grade I: under 1 degree above pre-treatment level.
Grade II: 1 to 2 degrees above pre-treatment level.
Grade III: 2 degrees or more above pre-treatment level.

SUMMARY

1. Four hundred and twenty-nine patients with darkfield positive syphilis were treated over a three and three-quarter day period, each receiving 1,200,000 units of sodium penicillin, given 40,000 units intramuscularly every three hours for 30 doses.

2. Eighty-five patients were considered treatment failures. (See "Failures," table 3.)

3. In our experience, this schedule of treatment appears to be more effective than smaller amounts of penicillin either alone or in combination with arsenicals administered over twice the time period.

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THE USE OF BAL (2,3–DIMERCAPTOPROPANOL) IN THE TREATMENT OF AGRANULOCYTOSIS FOLLOWING INTENSIVE ARSENOTHERAPY FOR SYPHILIS *

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Toxic reactions in man due to the systemic action of arsenic have been observed occasionally during routine arsenotherapy for syphilis. The recent widespread use of highly intensive schedules of anti-syphilitic treatment has markedly increased the incidence of these reactions. One of these, agranulocytosis, once considered rare, has occurred more frequently since these newer methods of arsenotherapy for syphilis have been introduced. This reaction, characterized by a disappearance of the granulocytes from the blood stream, is due possibly to the toxic action of arsenic on the blood forming organs. As a result of the loss of the granulocytes, infections occur more readily. Severe infections of the tonsils and pharynx are the most common in this condition. Treatment of this condition prior to the introduction of BAL consisted of the administration of blood transfusions, pentnucleotide and liver extract. The mortality rate of this toxic reaction has been very high, varying between 50 and 70 per cent.[1, 2] In the series of cases reported in this paper that were treated with BAL, no deaths occurred. Announcement of the development and properties of this substance has been withheld until recently for reasons of security.

BAL was first described by Peters.[3] It is an anti-arsenical, 2,3-dimercaptopropanol, that was first used by the British for Lewisite gas burns. It is from this that the name BAL (British Anti-Lewisite) is derived. Investigators have recently found that this compound is of value not only in the treatment of local arsenical reactions, but for systemic reactions as well.[4]

The toxicity of arsenicals has been shown to be due to the combination of the arsenic radical with the SH groups of the activating protein of enzyme systems to form a stable compound, which thereby interferes with tissue respiration.[5] BAL through its selective affinity for the arsenic radical may prevent or even reverse this reaction. The resulting compound is known as thio-arsenite, which is more stable and is easily excreted by the kidneys.

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The drug is dispensed in a stable solution using peanut oil with benzyl benzoate as a solvent. The dosage recommended is 2.5 mg. per kilo. at each injection. This is repeated every four hours for the first two days, then once or twice daily thereafter for six days. Adjuncts to this treatment are necessary to combat infection present in the majority of these cases. Doan [6] has shown through his studies on the correlation of bone marrow and peripheral blood observations that approximately two weeks may be required for the maturation of the immature myeloblast to the mature polymorphonuclear neutrophilic leukocytes. It is in this phase of the complication that the so-called "anti-biotic reprieve" is effective, and then only if the insult is of mild and temporary nature. Penicillin is the drug of choice used to effect this reprieve. If the damage to the bone marrow is so potent that the myelopoiesis is more than transiently impeded, this temporary suppression of secondary bacterial invaders is of no avail. Penicillin was used effectively in one instance but its unavailability at the time curtailed its further use.

Twelve cases of agranulocytosis occurring during arsenotherapy for syphilis were observed and all were treated with BAL. No mortality occurred in this series. All these cases occurred in patients treated with intensive arsenotherapy with the exception of one. In the latter case the complication occurred during routine therapy using neoarsphenamine. Mapharsen was the arsenical used in the remaining 11 cases.

Case 1. B. L., colored female, age 20, was admitted on June 3, 1944, with a diagnosis of early latent syphilis, previously treated, and gonorrheal cervicitis. She was placed on an intensive treatment schedule, consisting of 55 milligrams of mapharsen given intravenously daily, for a period of 25 days. At the same time she was given four grams of sulfathiazole daily for five days. On admission the hemoglobin was estimated at 77 per cent. The white count was 6,500, with no differential count recorded. The urinalysis was essentially normal.

The patient tolerated mapharsen well until the eighteenth injection, when she developed a sore throat and chilly sensations and a temperature of 102.2° F. On examination there was diffuse redness, edema of the pharynx, and several ulcerated areas on both tonsils. At this time the hemoglobin was 80 per cent, the red blood count 4,410,000, and the white blood count 3,000, with a complete absence of granulocytes, 87 per cent lymphocytes, and 13 per cent monocytes. Mapharsen was discontinued and treatment with BAL instituted. The temperature remained elevated for four days, reaching a peak of 103° F., after which it fell by lysis. Granulocytes reappeared within three days, at which time the hemoglobin was 82 per cent, the red blood count 4,400,000, and the white blood count 4,000, with 90 per cent polymorphonuclear neutrophiles, 1 per cent basophiles, 4 per cent lymphocytes, and 5 per cent monocytes. On the next day the white blood count was 6,600, with 24 per cent polymorphonuclear neutrophiles, 68 per cent lymphocytes, and 8 per cent monocytes. On the fifth day following reaction the white blood count was 9,600, with 56 per cent polymorphonuclear neutrophiles, 38 per cent lymphocytes, and 6 per cent monocytes. The patient made an uneventful recovery.

Case 2. O. F., colored male, age 39, was admitted on February 22, 1944, with a diagnosis of primary syphilis, seropositive, previously treated, and was placed on an intensive treatment schedule, receiving 70 milligrams of mapharsen daily for 20 days. An admission blood count was not done. The urinalysis was essentially normal.

The patient tolerated mapharsen well with the exception of mild headache and nausea following each injection. In addition to the mapharsen, he also received four grams of sulfathiazole a day for five days for the secondary infection in the primary lesion. Following the eighteenth injection of mapharsen the patient developed a temperature of 102.4° F. and complained of a sore throat. Examination revealed a necrotic lesion of both tonsils. The white blood count was 2,600, and there was a complete absence of granulocytes. He was given a 500 c.c. blood transfusion and started on BAL. The next day the white blood count was 1,000 and there was still a complete absence of granulocytes. He was given a second transfusion in 24 hours together with other supportive measures. He continued to run a septic temperature reaching 105° F. for six days, after which the temperature returned to normal. The granulocytes reappeared in the blood stream on the seventh day. Two weeks following reaction, the white blood count was 6,320, and there were 58 per cent polymorphonuclear neutrophiles, 38 per cent lymphocytes, and 4 per cent monocytes. The patient made an uneventful recovery.

Case 3. O. D., colored female, age 17, was admitted on August 11, 1944, with a diagnosis of early latent syphilis, not previously treated, with eight months' pregnancy. She was placed on an intensive treatment schedule, receiving 60 milligrams of mapharsen daily for 25 days. On admission the hemoglobin was 55 per cent and the white blood count was 7,200, with 65 per cent polymorphonuclear neutrophiles, 53 per cent lymphocytes, and 2 per cent monocytes. The urinalysis was essentially normal.

The patient tolerated mapharsen well until the twentieth dose, at which time in a routine blood count it was noted that the white blood count had fallen to 3,500, with 5 per cent polymorphonuclear neutrophiles, 3 per cent eosinophiles, 59 per cent lymphocytes and 3 per cent monocytes. She had no complaints. Examination revealed only a slight injection of the pharynx and the temperature was 100.8° F. Mapharsen was discontinued. On the second day after this reaction the patient went into labor and delivered a full-term living infant. She was treated with pentnucleotide, liver extract intramuscularly and BAL. She also received two 500 c.c. blood transfusions. The temperature dropped by lysis after the fourth day. The fifteenth day following the complication, the hemoglobin was 85 per cent, and the white blood count was 7,300, with 56 per cent polymorphonuclear neutrophiles, 2 per cent eosinophiles, 37 per cent lymphocytes, and 5 per cent monocytes. The patient made an uneventful recovery.

Case 4. E. G., colored female, age 18, was admitted on July 15, 1944, with a diagnosis of early latent syphilis, not previously treated, and was placed on an intensive treatment schedule consisting of 55 milligrams of mapharsen daily for 25 days. In the admission blood count the hemoglobin was 75 per cent, the white blood count was 6,300 and there were 60 per cent polymorphonuclear neutrophiles, 2 per cent eosinophiles, 36 per cent lymphocytes, and 2 per cent monocytes. The urinalysis was essentially normal.

The patient tolerated mapharsen well until the eighth dose, at which time the temperature rose to 102° F. The blood count and urinalysis showed no abnormal findings. Treatment was withheld for one day and small trial doses of mapharsen were given on the following three days without any rise in temperature, and so the full schedule was again resumed. Following the twentieth dose of mapharsen, a routine blood count showed the white blood count had fallen to 3,000, with a complete absence of granulocytes, 73 per cent lymphocytes and 27 per cent monocytes. At this time the temperature was elevated to 100.2° F. The patient, however, had no complaints. Mapharsen was discontinued. The following day the temperature rose to a peak of 103.6° F. and there was still an absence of granulocytes. The patient was placed on BAL and forced fluids. The temperature remained elevated for three days

and then returned to 99° F. Granulocytes reappeared in the circulating blood at the same time, so that within four days the hemoglobin was 73 per cent and the white blood count 6,400, with 44 per cent polymorphonuclear neutrophiles, 2 per cent eosinophiles, 44 per cent lymphocytes, and 10 per cent monocytes. The patient made an uneventful recovery.

Case 5. C. R., colored female, age 25, was admitted August 8, 1944, with a diagnosis of early latent syphilis, not previously treated, and was placed on an intensive schedule, receiving 55 milligrams of mapharsen daily for 25 days. On admission the hemoglobin was 60 per cent, the white blood count 6,000, with 65 per cent polymorphonuclear neutrophiles, 33 per cent lymphocytes, and 2 per cent monocytes. The urinalysis was essentially normal.

The patient tolerated mapharsen well. A routine blood count performed following the twentieth dose of mapharsen showed the white blood count 3,800, with no polymorphonuclear neutrophiles, 2 per cent eosinophiles, 58 per cent lymphocytes, and 50 per cent monocytes. The same evening there was a rise in temperature to 103° F. At the same time there was noted necrotic ulceration of the gingival tissue and a small eroded area on the right tonsil. Arsenotherapy was discontinued and the patient was placed on intramuscular liver, pentnucleotide, and BAL. The following days there was a complete absence of granulocytes. On the third day after the institution of treatment for the agranulocytosis, granulocytes reappeared. The white blood count was 4,500, with 15 per cent polymorphonuclear neutrophiles, 55 per cent lymphocytes, 30 per cent monocytes. Recovery was uneventful.

Case 6. L. C., colored female, aged 19, was admitted February 26, 1944, with a diagnosis of secondary syphilis, previously treated, and was placed on a 20-day schedule of intensive therapy, receiving 50 milligrams of mapharsen daily.

The patient tolerated mapharsen well until the tenth dose, at which time she complained of nausea and vomiting. It was noted at that time that the temperature was elevated to 100° F. and there was some injection of the conjunctivae. Treatment was withheld for one day, after which a small trial dose of mapharsen was administered. This was apparently well tolerated and treatment was resumed. Following the fifteenth dose of mapharsen, the patient developed a severe chill and her temperature rose to 105° F. Mapharsen was discontinued. Physical examination revealed marked pharyngitis. The blood count on the morning of the same day was 85 per cent hemoglobin, the white blood count was 6,100, with 65 per cent polymorphonuclear neutrophiles and 35 per cent lymphocytes. That night at 10:30 a repeat blood count revealed a white blood count of 2,000 and there were 10 per cent polymorphonuclear neutrophiles, 50 per cent lymphocytes, and 40 per cent monocytes. On the following day the red blood count was 4,200,000, the white blood count 2,450, with no polymorphonuclear neutrophiles, 2 per cent basophiles, 4 per cent eosinophiles, 47 per cent lymphocytes, and 47 per cent monocytes. The third day following this complication, the red blood count was 3,820,000, the white blood count 2,020, with a complete absence of granulocytes, 55 per cent lymphocytes, and 45 per cent monocytes. The patient experienced a stormy course with a septic temperature and necrotic pharyngitis. She was placed on BAL and penicillin with general supportive measures. On the eleventh day following the complication, the hemoglobin was 82 per cent, white blood count was 5,600, with 21 per cent polymorphonuclear neutrophiles, 75 per cent lymphocytes, and 4 per cent monocytes. The blood count returned to normal on the fourteenth day. The patient made an uneventful recovery.

Case 7. J. B. G., colored female, age 19, was admitted on June 12, 1944, with a diagnosis of a febrile reaction following the fourth injection of neoarsphenamine for the treatment of secondary syphilis while under the care of a private physician. On admission the patient appeared toxic, her temperature was 104° F., and she had necrotic ulcerative lesions of the pharynx and tonsils. The hemoglobin was 55 per

cent, red blood count 3,200,000 and the white blood count 4,800, with 14 per cent polymorphonuclear neutrophiles, 5 per cent eosinophiles, 61 per cent lymphocytes, and 20 per cent monocytes. These findings suggested the diagnosis of agranulocytosis. A blood count on the following day was essentially the same. The patient was placed on pentnucleotide, BAL and other supportive measures. The temperature remained elevated for one week and fell by lysis. During this period the number of granulocytes increased so that one week after admission, the white blood count was 12,400, with 76 per cent polymorphonuclear neutrophiles, 1 per cent eosinophiles, 21 per cent lymphocytes and 2 per cent monocytes. The pharyngitis cleared up rapidly and the patient made an uneventful recovery.

Case 8. H. P., colored female, age 17, was admitted on October 9, 1944, with a diagnosis of early latent syphilis, previously treated, and was placed on a 25-day intensive treatment schedule, receiving 50 milligrams of mapharsen daily. In the admission blood count there was 90 per cent hemoglobin, the white blood count was 6,300, with 60 per cent polymorphonuclear neutrophiles, 38 per cent lymphocytes, and 2 per cent monocytes. The urinalysis was essentially normal.

The patient tolerated mapharsen well until the ninth dose, at which time she complained of itching of the feet and back, but no eruption could be seen. The temperature was elevated to 100.6° F. At this time the hemoglobin was 88 per cent, the white blood count was 4,600, with 38 per cent polymorphonuclear neutrophiles, 58 per cent lymphocytes, and 4 per cent monocytes. Mapharsen was withheld for one day, following which she received a small trial dose, from which there was no apparent reaction. Treatment was then resumed with the full dose of mapharsen without difficulty until she had received the thirteenth injection. The temperature then rose suddenly to 104.6° F. and the patient complained of general malaise and sore throat. The hemoglobin was 87 per cent, the white blood count 3,600, with 6 per cent polymorphonuclear neutrophiles, 82 per cent lymphocytes, and 12 per cent monocytes. There was a moderate pharyngitis and a grayish exudate covering both tonsils. Mapharsen was immediately discontinued, and the patient was placed on BAL and forced fluids. The temperature remained elevated for three days, after which it returned to normal, and by the fourteenth day the hemoglobin was 88 per cent and the white blood count was 5,000, with 46 per cent polymorphonuclear neutrophiles, 1 per cent eosinophiles, 39 per cent lymphocytes, and 14 per cent monocytes. The patient made an uneventful recovery.

Case 9. J. D., colored male, age 19, was admitted with a diagnosis of secondary syphilis, previously treated, and acute gonorrheal urethritis. The previous treatment consisted of 0.3 gram of neoarsphenamine and 20 grams of sulfathiazole. He was placed on the penicillin-mapharsen-bismuth schedule, receiving 60 milligrams of mapharsen daily for eight consecutive days. On admission the hemoglobin was 95 per cent and the white blood count 6,000, with 52 per cent polymorphonuclear neutrophiles and 48 per cent lymphocytes. The urinalysis was essentially normal.

The patient tolerated mapharsen well until the sixth dose, at which time the temperature was elevated to 102.6° F. The white blood count at this time was 7,000, with 75 per cent polymorphonuclear neutrophiles and 25 per cent lymphocytes. Although mapharsen was omitted, the temperature contined to rise and reached a peak of 105° F. within 48 hours and then fell by lysis, reaching normal on the sixth day after the onset of the reaction. On the tenth day following discontinuance of arsenotherapy, the patient was again given 60 milligrams of mapharsen. The next day the last and eighth dose of mapharsen was given. The temperature immediately rose to 101° F., and the white blood count was 3,800, with 5 per cent polymorphonuclear neutrophiles, 11 per cent eosinophiles, 74 per cent lymphocytes, and 10 per cent monocytes. The patient was placed on intramuscular liver extract and BAL. Four days later the white blood count was 4,800, with 4 per cent polymorphonuclear neutro-

philes, 9 per cent eosinophiles, 63 per cent lymphocytes, and 24 per cent monocytes. Daily blood counts showed a progressive rise in the leukocytes as well as in the percentage of granulocytes.

During this whole episode the patient was never very uncomfortable, nor did he ever develop pharyngitis. The white blood count on discharge two weeks after the onset of symptoms was 8,000, with 64 per cent polymorphonuclear neutrophiles and 36 per cent lymphocytes.

Case 10. G. R., colored female, age 15, was admitted on July 17, 1944, with a diagnosis of early latent syphilis, not previously treated, and was placed on a 25-day intensive treatment schedule, receiving 50 milligrams of mapharsen daily. On admission, the red blood count was 3,600,000, the white blood count was 10,000, with 69 per cent polymorphonuclear neutrophiles and 31 per cent lymphocytes. The urinalysis was essentially normal.

The patient tolerated mapharsen well until the seventh dose, when she complained of headache and the temperature was elevated to 100° F. The patient remained on treatment in spite of this elevation, which continued until the eleventh dose of mapharsen. At this time there appeared on the extensors of the forearms and thighs a fine papular non-pruritic eruption. The temperature was again 100° F. This was interpreted as an erythema of the ninth day. Mapharsen was withheld for two days, after which treatment was resumed. Following the fifteenth dose there was a brisk rise in temperature to 102.2° F., and she complained of a sore throat. The following day a necrotic exudate was found in the pharynx. On this day the red blood count was 3,850,000 and the white blood count 3,800, with no polymorphonuclear neutrophiles, 2 per cent eosinophiles, 78 per cent lymphocytes, and 20 per cent monocytes. Treatment consisted of BAL and general supportive measures. The patient's temperature remained septic for the next three days and returned to normal by lysis on the fifth day. On that day granulocytes reappeared in the blood and there were 7,400 white blood cells, with 54 per cent polymorphonuclear neutrophiles, 10 per cent eosinophiles, 30 per cent lymphocytes, and 6 per cent monocytes. The patient made an uneventful recovery.

Case 11. E. W., colored female, age 18, was admitted on September 9, 1944, with a diagnosis of secondary syphilis, not previously treated, with pregnancy, and was placed on a 25-day intensive treatment schedule, receiving 55 milligrams of mapharsen daily. On admission the hemoglobin was 78 per cent, the white blood count 8,500, with 63 per cent polymorphonuclear neutrophiles and 37 per cent lymphocytes. The urinalysis was essentially normal.

The patient tolerated mapharsen well with the exception of a daily elevation of temperature between 99° F. and 100° F. Following the nineteenth injection of mapharsen, there was a brisk rise in temperature to 102.4° F. The patient complained of a sore throat. On examination she was found to have a necrotic membrane on both tonsils and large tender cervical lymph nodes. At this time the hemoglobin was 77 per cent, the white blood count 3,100, with 7 per cent polymorphonuclear neutrophiles, 68 per cent lymphocytes, and 25 per cent monocytes. Mapharsen was discontinued and the patient was placed on BAL. The following day the white blood count was 3,700, with 5 per cent polymorphonuclear neutrophiles, 65 per cent lymphocytes, and 30 per cent monocytes. The temperature remained elevated for five days and returned to normal by lysis. At the same time the granulocytes increased rapidly, so that by the fifth day following the complication the white blood count was 8,500, with 50 per cent polymorphonuclear neutrophiles, 40 per cent lymphocytes and 10 per cent monocytes.

Case 12. H. C., colored female, age 18, was admitted on April 24, 1944, with a diagnosis of secondary syphilis, not previously treated, and was placed on a 25-day intensive treatment schedule, receiving a daily dose of 55 milligrams of mapharsen.

On admission the hemoglobin was 82 per cent and the white blood count 6,400. No differential count was recorded. The urinalysis was normal. Following the nineteenth injection of mapharsen the patient complained of chilly sensations and dysphagia. The temperature was elevated to 102.4° F., the pharynx was reddened and edematous, and there was a necrotic membrane over the tonsils. The cervical lymph nodes were enlarged and tender. The hemoglobin was 75 per cent, the red blood count 4,300,000, the white blood count 4,100, with a complete absence of granulocytes, 60 per cent lymphocytes and 40 per cent monocytes. A smear taken from the pharynx showed a few fusiform bacilli, a moderate number of large spirochetes and a few pus cells. Mapharsen was discontinued, and the patient was placed on BAL, pentnucleotide, and liver extract. In addition she was given two blood transfusions. On the fifth day, the temperature fell by lysis, and the peripheral blood showed a few granulocytes for the first time. On the ninth day the patient was afebrile and the white blood count was 7,700, with 38 per cent polymorphonuclear neutrophiles, 10 per cent eosinophiles, 40 per cent lymphocytes, and 12 per cent monocytes. The patient made an uneventful recovery.

Discussion

The histories of these patients were not unusual. None gave a history of sensitivity to any drug, although 50 per cent of the cases had been previously treated with arsenicals. The type of onset in most of the cases was classical, with general malaise, headache, fever and sore throat. However, in two cases there was no pharyngitis, either concomitant with or after the febrile reactions. The reaction occurred in the last half or near the end of treatment in the majority of cases.

Routine blood counts were normal on admission with the exception of Case 7, who was admitted with agranulocytosis. The blood picture in all the cases developing the reaction showed a leukopenia with complete absence or marked reduction of granulocytes.

The course of illness was variable, Cases 2, 6 and 10 being highly toxic, having a stormy course; the others showing milder symptoms of toxicity. The blood counts returned to normal soon after the febrile reaction had been dissipated.

Treatment was routine in all cases. BAL was given in 1.5 c.c. (10 per cent solution) doses every six hours for 48 hours; then 2 c.c. daily for six doses. In three cases multiple blood transfusions were administered. In addition to this, the following general supportive measures were given: 5 per cent dextrose solution intravenously to maintain the water balance; sodium perborate mouth washes to decrease secondary infection; and vitamin therapy. In some of the cases pentnucleotide and liver extract were given.

Inasmuch as the majority of these patients received conventional supportive treatment, clinical evaluation of the efficacy of BAL is difficult. Indeed, this is true in view of the fact that it was not feasible to carry on a control series of patients with the same disease but receiving no BAL. In spite of these difficulties, the results obtained suggest that BAL, administered early, and in proper dosage, may contribute to and accelerate the recovery

of patients having agranulocytosis caused by the parenteral administration of arsenical drugs. This may be explained by the fact that BAL, through its selective affinity for the suppressing agent, may decrease the time that is required for the bone marrow to return to its normal function.

BAL is not an innocuous drug. If the dosage level of under 3 mg./kilo. is adhered to, toxic reaction rarely occurs. But when this dosage is exceeded,[8] some or all of the following reactions may occur: nausea, vomiting, headache, generalized aches and pains, burning sensations in the mouth, nose and eyes; sweating, restlessness, pain in the limbs, joints and trunk muscles. These untoward reactions to BAL seldom persisted for more than 30 minutes.

Conclusions

Twelve cases of agranulocytosis occurring during arsenotherapy of syphilis are reported. Immediate cessation of the arsenical, and early treatment with BAL was instituted. There were no deaths. The results herein described clearly reflect the therapeutic action of BAL and indicate also the necessity for both prompt and adequate treatment in order to decrease the mortality in this complication occurring in arsenical therapy.

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THE PROGNOSIS OF THE WOLFF–PARKINSON–WHITE SYNDROME *

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Many authors, including Wolff, Parkinson and White,[1] consider the prognosis of the Wolff-Parkinson-White syndrome (characterized by White et al.[1] essentially as: (1) a short P–R interval, (2) prolonged and deformed QRS complexes, (3) normal P–J interval, and a tendency to paroxysmal tachycardia) benign. However, in reviewing the literature there is considerable evidence to show that such is not always the case. Although this condition is frequently found on routine electrocardiographic study of patients with no cardiac complaints or physical abnormalities, it is often found in persons who have had cardiac complaints for many years. The chief complaint is palpitation and tachycardia, the latter being paroxysmal tachycardia of auricular, nodal or ventricular origin. Occasionally, other evidences of heart disease are found, which are often coincidental.

If the paroxysmal tachycardia does not occur too often or last too long the prognosis is good, but in some patients the syndrome has resulted in death. In other instances, patients with the Wolff-Parkinson-White syndrome have met with a cardiac type of death although the exact mechanism has not been ascertained. Eight patients have been collected with the Wolff-Parkinson-White syndrome who have died a cardiac type of death and in whom it is considered that the syndrome was responsible. For this reason we believe that this condition should be regarded as strongly suggestive or definite evidence of heart disease, and at least a responsible representative member of the family should have the cardiac state adequately explained and the serious possibilities indicated.

The literature reviewed revealed six instances of death, two of which were probably the result of this syndrome and four undoubtedly due to it. To this group we add two patients, one death probably due to the syndrome and another directly due to the paroxysmal tachycardia associated with the syndrome. F. N. Wilson [2] in 1938 reported a patient who died during an attack of paroxysmal tachycardia with no evidence of heart disease other than the presence of the Wolff-Parkinson-White syndrome. Vakil [3] in 1942 reported a patient with the syndrome complicated by mitral stenosis who died of congestive failure resulting from frequent prolonged attacks of paroxysmal tachycardia. In 1943 Nielsen et al.[4] reported a patient with paroxysmal tachycardia associated with the Wolff-Parkinson-White syndrome resulting in death. Wood, Wolferth and Geckeler [5] reported in 1943 a 13 year old

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boy with this syndrome who died of congestive heart failure two hours following the onset of an attack of paroxysmal tachycardia precipitated by drinking a glassful of cold water. Richard F. Ohnell [6] reported two fatalities in cases presenting the syndrome, one occurring during an attack of tachycardia and the other probably as a result of paroxysmal tachycardia.

Case Reports

A brief summary of the two additional patients who met a cardiac type of death is presented below:

Case 1. A white female patient, age 38, of Dr. J. M. Bamber had complained of attacks for several years of palpitation and rapid heart rate which had become more frequent of late. An electrocardiogram on April 29, 1935 showed an auricular

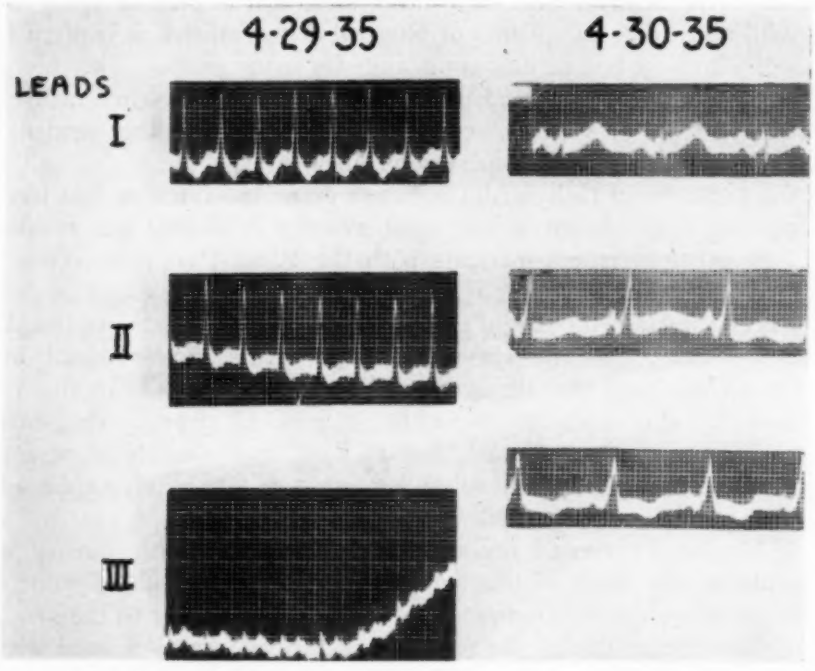

Fig. 1. The electrocardiograms of Case 1 showing a supraventricular paroxysmal tachycardia on April 29, 1935 and the Wolff-Parkinson-White syndrome on the next day when a normal sinus rhythm was established.

paroxysmal tachycardia with a rate of 240. Following quinidine therapy the rate returned to normal and the electrocardiogram showed a typical Wolff-Parkinson-White syndrome with a PR interval of 0.09 second and a QRS interval of 0.12 second (figure 1). Physical examination failed to reveal any abnormalities. Two weeks later she was found dead in bed. We assume that she died a cardiac death. Certainly it is safe to suspect a relation of the death to the Wolff-Parkinson-White syndrome.

Case 2. A male patient of Dr. Ralph Platou * born normally on May 21, 1944. On June 20, 1944 he was normal on physical examination with the exception of a rapid heart which the mother had first noted at the age of two weeks. A teleroentgenogram showed a normal cardiac configuration. Paroxysms of rapid heart rate occurred at intervals of two weeks, and lasted for 12 to 24 hours, the rate usually being about 250.

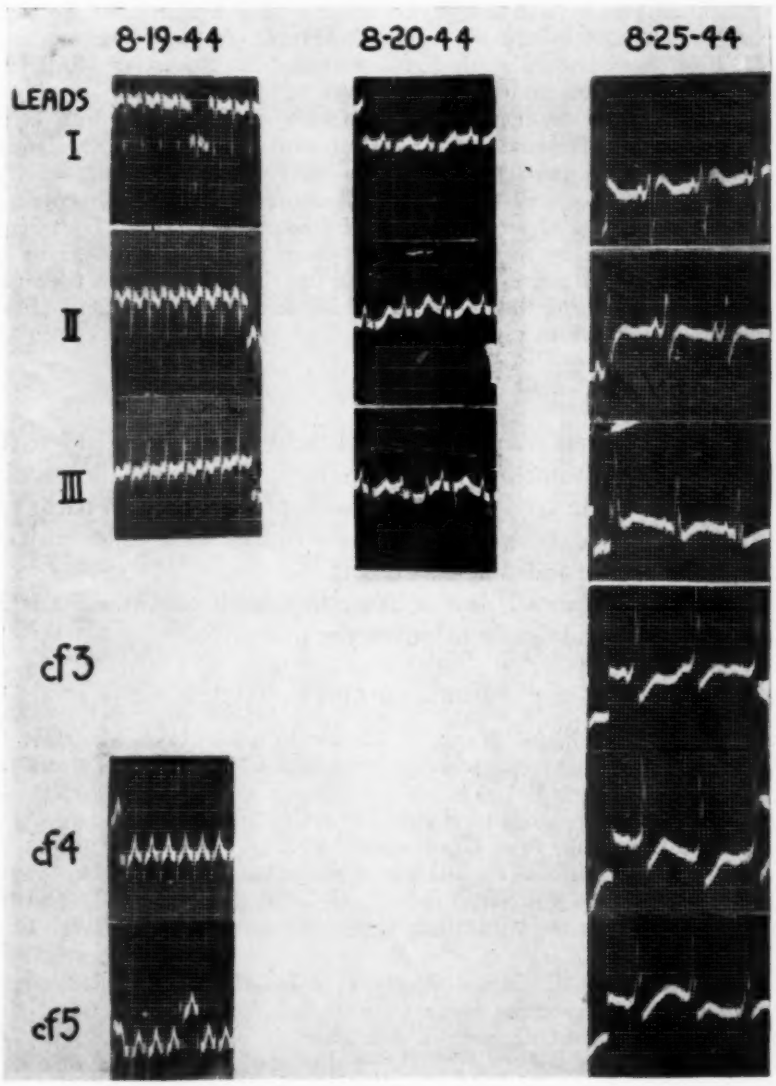

FIG. 2. The electrocardiograms of Case 2 showing a paroxysmal supraventricular tachycardia on August 19, 1944, a normal sinus rhythm with a normal conduction on August 20, 1944 and the Wolff-Parkinson-White syndrome and conduction through the aberrant bundle five days later.

* The authors wish to express their appreciation to Drs. J. M. Bamber and Ralph Platou of Tulane Medical School for granting permissions to report these patients.

August 20, 1944 the child was hospitalized because of decompensation. He was digitalized. During his stay in the hospital electrocardiograms were recorded (figure 2). The tracing of August 19, 1944 showed paroxysmal supraventricular tachycardia. On August 20, 1944 an electrocardiogram showed a sinus tachycardia with a normal mechanism and conduction. An electrocardiogram on August 25, 1944 showed the Wolff-Parkinson-White pattern.

The attacks of paroxysmal tachycardia became more frequent and lasted longer and the congestive heart failure became more severe. A teleroentgenogram dated October 31, 1944 showed slight cardiac enlargement. On November 16, 1944 quinidine sulfate was administered during an episode of tachycardia.

On January 16, 1945 another paroxysm of tachycardia resulted in a heart rate of 170–200 per minute. The next day the patient went into syncope. On January 18, generalized convulsions began at 3:00 p.m. and continued until death at 4:00 p.m.

The autopsy showed a well developed, well nourished infant with no abnormalities on gross examination of any organs, except acute dilatation of both ventricles. Examination of the heart by serial sections has been made.[7] Two aberrant bundles of muscle tissue have been found, one connecting the right atrium with the right ventricle and another connecting the left atrium to the left ventricle. The details of the histologic examination will be reported later.

Summary

Five deaths resulting from paroxysmal tachycardia secondary to Wolff-Parkinson-White syndrome and three additional deaths in patients with the Wolff-Parkinson-White syndrome which were probably due to paroxysms of tachycardia have been discussed. Six of the deaths were collected from the literature and two were added by this report.

With such a number of deaths associated with the Wolff-Parkinson-White syndrome it is advisable to guard the prognosis.

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BRONCHOGENIC CARCINOMA—A CLINICAL-PATHOLOGICAL STUDY OF 36 AUTOPSIED CASES SEEN AT THE BROOKLYN CANCER INSTITUTE BETWEEN 1937 AND 1945, INCLUSIVE *

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IN recent years, because of its undoubted increase in incidence and because early recognition may lead to cure by pneumonectomy, bronchogenic carcinoma has become an increasingly important clinical entity.

This report is based on the study of a series of 36 autopsied cases of bronchogenic carcinoma seen at the Brooklyn Cancer Institute between 1937 and 1945.

INCIDENCE

The literature of the past 10 years is replete with references to the question: Has a real increase in lung cancer been proved? The question has been reviewed exhaustively in the comprehensive monographs by Fried [1] and Simons.[2] Analysis of a total of 62,802 collected necropsies [3] would suggest a twenty-fold increase in lung cancer between 1900 and 1925.

Year	Relation of Primary Lung Cancers to all Cancers
1896–1901	0.54%
1902–1916	5.02%
1914–1919	6.36%
1920–1925	10.30%

It has been stated that since bronchogenic carcinoma is a disease of old age and since the average life expectancy has risen rapidly, an increase in the incidence of bronchogenic carcinoma should not be unexpected. However, Rosahn, in a careful statistical study, reached the conclusion that "the increase in pulmonary cancers observed in our autopsy material was a real and absolute increase." [4] This increase was definitely greater than that occurring in other malignancies.

Macklin,[5] applying rigidly logical criteria to the problem, has concluded that "We can merely state that *diagnosed* lung cancer is increasing at a rate which appears to be faster than that of other *diagnosed* cancers."

Peery [6] has emphasized two infrequently-realized facts: (1) Carcinoma of other areas can be metastatic to bronchial epithelium. (2) All the tumors formerly designated by the terms "endothelioma of the pleura," "oat-cell tumor of the mediastinum" and "tumor of the superior pulmonary sulcus" are now included in the classification of bronchogenic carcinoma, thus

* Received for publication January 31, 1947.

swelling the statistics rather than increasing the actual incidence of the disease.

Regardless of the apparence or reality of the increase, the fact remains that bronchogenic carcinoma which was a clinical curiosity 50 years ago, has become one of the most frequently-diagnosed diseases of the lung today.

Koletsky [7] reviewed autopsies performed at the Cleveland City Hospital in the eleven-year period from 1927 to 1937, inclusive. There were 100 cases of primary carcinoma of the lung, constituting 1.3 per cent of 7,685 consecutive cases studied post mortem and 9.4 per cent of 1,064 cases of malignant tumor studied post mortem. At autopsy the lung ranked second only to the stomach as the primary site of carcinoma.

Jaffe,[8] in a similar study of 100 autopsied cases of primary carcinoma of the lung, found the lung to be the primary site in 11.4 per cent of 876 cases of malignant tumor found in a series of 6,800 consecutive autopsies. The lung ranked third, stomach first, large intestine second.

TABLE I

Common Primary Sites of Malignancy

Primary Site		Number	Per Cent
1. Breast		75	18
2. Lung		38	9
3. Large intestine		33	7
4. Stomach		29	6
5. Cervix		28	6
6. Intraoral and pharyngeal		24	5
Tonsil	7		
Hypopharynx	6		
Palate and alveolar ridge	6		
Nasopharynx	3		
Buccal mucosa	2		
7. Non-malignant		20	5
8. Lymphosarcoma		19	4
9. Tongue		17	4
10. Bladder		14	3
11. Esophagus		13	3
12. Larynx		13	3
13. Hodgkin's disease		11	2
14. Pancreas		11	2
15. Others		99	23
Total		444	100

Of 444 autopsies performed at the Brooklyn Cancer Institute between 1937 and 1945, inclusive, bronchogenic carcinoma was found in 38 cases, an incidence of 8.6 per cent of all autopsies performed and 9.0 per cent of cases of malignancy studied post mortem. Two of these 38 cases are not included in the present report.

Many of the patients seen at this hospital are referred for radiation therapy. An analysis of the more common primary sites seen at autopsy reflects this fact in the abnormally high incidence of breast, intraoral and pharyngeal malignancies, lymphosarcoma and Hodgkin's disease (table 1).

Bronchogenic carcinoma is characteristically a disease of males who comprise 75 to 90 per cent of most reported series.[1, 2, 9, 10] In our series there were 32 males, an incidence of 88 per cent.

The age incidence of bronchogenic carcinoma is significantly lower than that of many common malignancies.

TABLE II

Mean Age of Persons with Carcinoma of Various Sites [4]

	Number of Cases	Mean Age
Prostate	32	71.5 ± 1.9
Liver and bile ducts	26	62.7 ± 2.19
Esophagus	27	61.1 ± 1.60
Rectum and sigmoid	52	57.8 ± 1.55
Stomach	58	57.7 ± 1.41
Lung	43	55.0 ± 1.58
Uterus	29	52.2 ± 1.99

The mean age in our series was 55.1 years, almost half the cases occurring in the sixth decade.

TABLE III

Sex and Age Incidence—Present Series

	Number	Per Cent
Sex:		
Male	32	88
Female	4	12
Age:		
30–39	1	3
40–49	8	22
50–59	16	44
60–69	11	31

Mean age: 55.1 years.

PATHOLOGICAL, ROENTGENOLOGICAL AND CLINICAL CONSIDERATIONS

All primary bronchogenic carcinomas arise from an undifferentiated stem cell located in the basal layer of the bronchial epithelium. The tumor is an adenocarcinoma, a squamous-cell carcinoma or an undifferentiated or anaplastic carcinoma, depending on the type and degree of differentiation of the original stem cell. Tumors falling into the different histological categories have similar clinical courses, metastasize in a similar manner and show no consistent variations in their response to radiation therapy. Different series, classified by equally competent pathologists, show tremendous variations [9, 19, 23, 25] in the percentages of the various histological types. For these reasons such classifications may be regarded as of academic rather than of practical significance.

The earliest and most common symptom, frequently overlooked for months, is a non-productive cough. The growing tumor is a foreign body which the bronchus attempts to extrude. Soon a clear, mucoid sputum appears as the irritated bronchial epithelium attempts to wash out the foreign body. The continuous trauma of coughing together with degeneration of

the tumor produces ulceration of the surface of the growing tumor with the production of blood-streaked or purulent sputum. Because most bronchogenic carcinomas originate in the major bronchi positive diagnosis by bronchoscopic biopsy is often possible at this time. Physical examination and chest roentgenograms show no evidence of the disease in this stage.

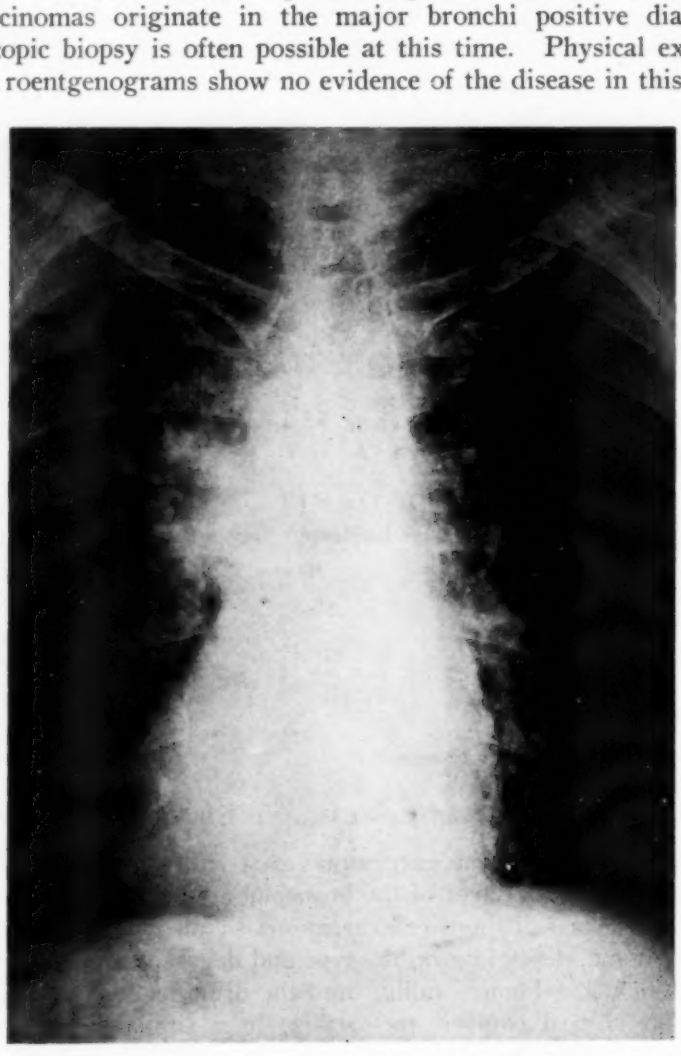

FIG. 1. Typical roentgenographic sequence in bronchogenic carcinoma. (*a*) March 3, 1945, tumor mass arising from left upper hilus.

The inspiratory phase of respiration is more powerful than the expiratory phase. Consequently, as the growing tumor begins to cause partial obstruction of the bronchus, the segment of lung distal to the affected bronchus becomes emphysematous. Wheezing or asthmatic breathing may appear. The development of asthmatic breathing in middle-aged individuals should initiate a thorough search for bronchogenic carcinoma. Rarely during this stage of partial bronchial obstruction a hyperresonant percussion note, em-

physematous breath sounds and expiratory râles and rhonchi may be found on physical examination, while the roentgenogram may disclose a wedge-shaped area of decreased density with convex limiting borders.

Usually this period of emphysema is of short duration and remains unrecognized while the enlarging tumor gradually produces complete bronchial

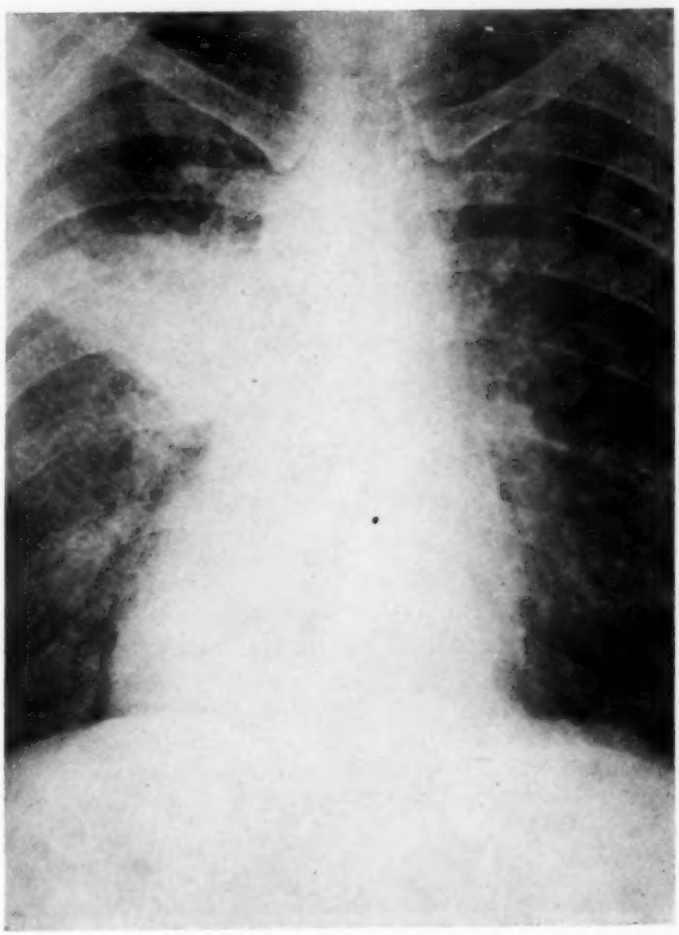

FIG. 1*b*. July 5, 1945, dense, wedge-shaped area of atelectasis extending beyond the tumor mass to the periphery of the lung.

obstruction and atelectasis. If the occluded bronchus is sufficiently large there may be a considerable shift of the mediastinum to the affected side, there is a real decrease in functioning lung volume and dyspnea will develop.

Almost simultaneously secondary infection develops within the atelectatic segment as necrotic tumor tissue, mucus, pus and bacteria accumulate. Leukocytosis, fever and anemia appear at this time and persist virtually un-

alterable until death. We have been impressed by the frequent early appearance of this triad, which will be discussed below.

In many cases this relentless course is interrupted by breakdown of part of the obstructing tumor. Necrotic tissue and pus are expectorated and fever and leukocytosis disappear. But tumor growth continues and leads to

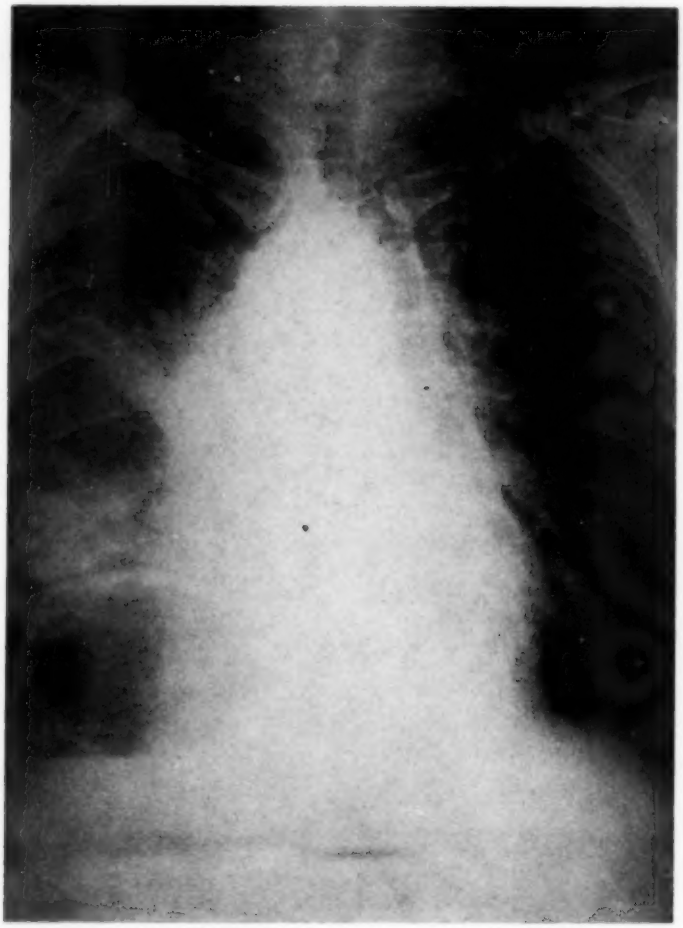

FIG. 1*c*. November 9, 1945, phrenic nerve involvement with elevation of the left half of the diaphragm and partial atelectasis of the left lower lobe.

further bronchial obstruction with secondary infection. This cycle is responsible for the dangerous diagnosis of "recurrent pneumonia" which has been made too frequently in the face of an advancing malignancy.

The earliest and most frequent pathologic change producing physical signs is atelectasis. Over the atelectatic area diminished or absent tactile fremitus, dullness on percussion and diminished breath sounds of bronchovesicular or bronchial quality, are found. On fluoroscopy all findings, such

as mediastinal shift to the atelectatic side on inspiration, elevation of the diaphragm, paradoxical elevation of the diaphragm on inspiration and narrowing of the intercostal spaces, are the result of atelectasis. The atelectatic area itself is a dense wedge-shaped shadow with relatively indefinite concave borders extending from the hilus toward the chest wall. Fluoroscopy reveals the abnormalities in respiratory dynamics; roentgenograms supply the permanent record. At this stage the tumor itself is seen in relatively few hilar cases but in most of the less common peripherally-located growths (figure 1).

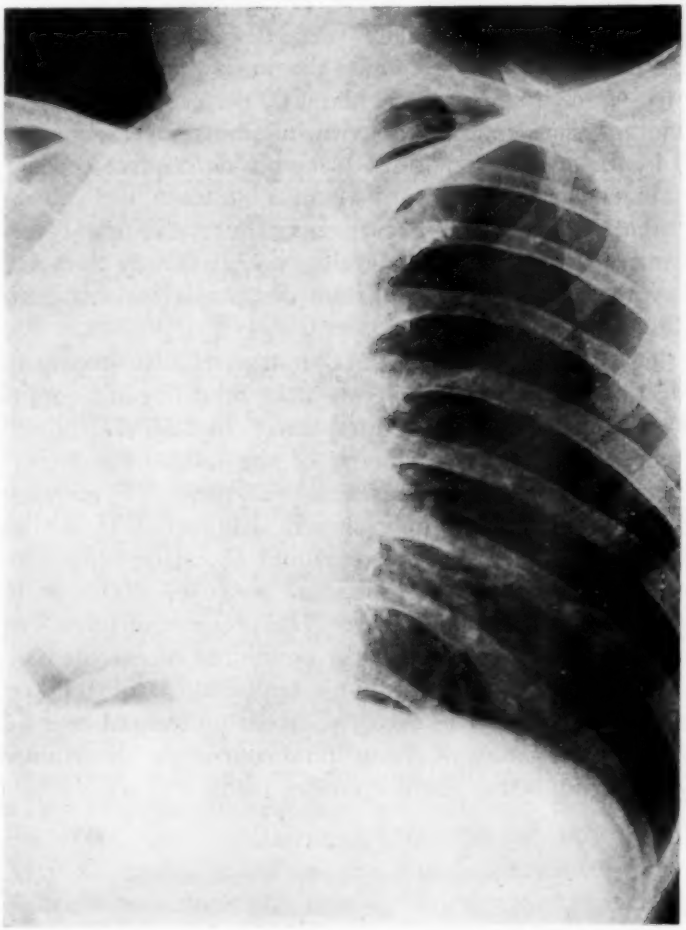

FIG. 2. Characteristic roentgenographic appearance following complete occlusion of the left main bronchus by tumor tissue. There is a homogeneous opacity throughout the left hemithorax, the heart, mediastinum and trachea are drawn to the atelectatic side, the left half of the diaphragm is elevated and the intercostal spaces are narrowed on the left.

Within the atelectatic areas lung tissue is destroyed by infection and tumor growth until a lung abscess which is often indistinguishable from the

usual pyogenic lung abscess develops. Not infrequently tumor cells reach the pleura where they produce a reactive hemorrhagic pleural effusion. In time sputum is aspirated into other bronchi producing numerous areas of bronchitis and pneumonitis. The physical and roentgenologic findings are those consistent with the pathological processes described (figure 2).

Roentgenological diagnosis is not always easy. Olds and Kirklin [23] who reviewed 206 microscopically verified cases, found that the roentgenologist was able to make a definite diagnosis of bronchogenic carcinoma or at least to suggest its presence in about 60 per cent. In the remaining 40 per cent findings were confounded with inflammatory lesions of the thorax in one-third. In another one-third a merely descriptive report was made. In the remainder various diagnoses—lymphoblastoma, metastatic carcinoma, interlobar fluid, tuberculosis, aneurysm or "negative chest"—were made.

In too many cases the tumor develops so insidiously that the presenting signs and symptoms are those of distant metastasis or local mediastinal extension. These will be considered later.

Fever, leukocytosis and anemia, characteristically accompanying many chronic infectious processes, are frequent in bronchogenic carcinoma. Yet they are barely mentioned in the literature. In 1877 Darolles [13] described the occurrence of fever in carcinoma of the lung. Hamman [12] in 1933, placed great emphasis upon the presence of fever. "Fever deserves to be mentioned on account of its importance in diagnosis. It is always present at late stages of the disease and sometimes at earlier stages as well. At early stages it is usually inconspicuous, not over 100° or thereabouts; at later stages it is often much higher. The presence of fever frequently dissuades physicians from considering the possibility of carcinoma."

In the present series a maximum temperature of 99° occurring at some time during the day was accepted as within normal limits. The temperature range during most of the hospital course was determined as closely as possible, ignoring acute febrile episodes (table 4).

TABLE IV

Temperature Level during Hospitalization

	Number of Cases	Per Cent
Normal	8	22
99–100° F.	11	30
99–101	9	25
99–102	5	14
98–103	3	9
Total	36	100

The most frequently seen fever curve was completely irregular, reaching 100 or 101° at some time on most days. In eight cases the fever curve was more typically septic, rising to 102 or 103° late in the day after being normal or subnormal in the morning.

Paralleling fever roughly, the white cell count was frequently elevated with a moderate to marked shift to the left (table 5).

TABLE V
Variations in White Cell Count

Total White Count	Highest	Lowest	Only Count	Not Done
Less than 10,000	1	8	5	
10–20,000	10	7	10	
20–30,000	2	1	2	
More than 30,000	3			
Total	16	16	17	3

In 16 cases multiple counts were performed. While in no case was a count higher than 30,000 white cells per cu. mm. maintained indefinitely, one leukemoid reaction was observed, in which the white cell count rose to 85,800 and dropped gradually to 30,000 during a three-month interval. Examination of the sternal marrow showed only marked leukocytosis and was suggestive of an irritative bone marrow process. Bone metastases visible by roentgenogram appeared five months after the height of the leukemoid reaction. Lisa, Solomon and Gordon [14] and Jackson [15] have reported similar leukemoid reactions in bronchogenic carcinoma.

TABLE VI
Red Cell Count

Red Cell Count	Number
Less than 3,000,000 on one occasion	5
Less than 4,000,000	24
4–5,000,000	6
More than 5,000,000	3
Not done (terminal on admission)	3

The occurrence of anemia is mentioned only casually, if at all, in most discussions of bronchogenic carcinoma. Although rarely profound it is quite common. A count of less than 4,000,000 red cells per cu. mm. was found in 24 of 33 cases who had repeated blood counts during their hospitalizations. There was a slight but definite tendency toward increasing anemia terminally (table 6).

TABLE VII
Final Clinical Diagnosis

Diagnosis	Number of Cases
Bronchogenic carcinoma	31
Metastatic carcinoma (primary site unknown)	2
Carcinoma of rectum	1
Lymphosarcoma of mediastinum	1
Sarcoma of chest wall	1
Total	36

Diagnosis

The diagnosis of bronchogenic carcinoma is frequently a difficult diagnosis to prove. It is of interest to examine the final diagnoses in this series of 36 cases, most of which had had several admissions to the hospital and thorough study. On five occasions the correct diagnosis was missed (table 7).

While it is rather a disturbing experience in this era of refined diagnostic technics to find a percentage of missed diagnoses as great as 14 per cent there is consolation to be found in a brief analysis of the diagnostic errors.

1. J. K. was a white male 56 years of age whose presenting symptom was swelling in the right groin shown to be an osteolytic metastasis to the right ilium. The biopsy report was anaplastic carcinoma. Although chest roentgenograms showed a mass bulging into the left lung field from the left supracardiac shadow—"probably primary bronchogenic carcinoma of the left main bronchus" according to the roentgenologist —no tumor tissue was seen on bronchoscopy. Final clinical diagnosis: Metastatic anaplastic carcinoma, primary site unknown.

At autopsy the left main bronchus was the seat of a large primary adenocarcinoma.

2. V. T. was a white male 38 years of age whose presenting symptoms were chills, night sweats, fever, substernal pain. The original chest roentgenogram taken at a district health center was reported as suggestive of pulmonary neoplasm. Bronchoscopy revealed no tumor tissue. A soft-tissue mass removed from the right thigh was diagnosed as a sarcoma microscopically. Subsequent involvement of the anterior chest wall occurred.

Final clinical diagnosis: Sarcoma of chest wall?
Carcinoma of lung?

At autopsy an anaplastic carcinoma originating in the left upper lobe bronchus was found. There were widespread metastases.

3. B. B. was a white male 61 years of age whose presenting sign was a rectal mass erroneously reported as adenocarcinoma of the rectum at another hospital. Bronchoscopy was never performed. Chest roentgenograms showed an enlarged right hilus node and terminally, consolidation of the entire right lung. Repeat biopsy of the rectal mass and biopsy of a facial nodule were both reported as anaplastic carcinoma.

Final clinical diagnosis: Carcinoma of rectum.

At autopsy an anaplastic carcinoma primary in the right lower lobe bronchus was found. There were widespread metastases to various organs including the skin and the rectal wall.

4. T. S. was a white female 49 years of age whose presenting symptom was severe low back pain of sudden onset which improved after one week of bed rest. Pain severe enough to confine the patient to bed and radiating down the back of the right thigh and leg recurred four months later. Shortly thereafter a cordotomy was performed at another hospital because of the intensity of the pain. The diagnosis at that time was: Carcinoma of unknown primary site with metastases to the pelvis and lumbar vertebrae. Ten months after the onset of pain, paraplegia developed. Roentgenograms showed a pathological compression fracture of the body of the third lumbar vertebra. It is interesting to note that at no time was a roentgenogram of the chest taken.

At autopsy an adenocarcinoma, peripherally placed in the left lower lobe, was found with metastases to nothing but the third, fourth and fifth lumbar vertebrae.

5. H. S. was a white male 50 years of age whose presenting symptoms were cough and left subcostal pain. Roentgenograms showed only a widened mediastinum. Bronchoscopy was not performed. Radiation therapy was not given until six weeks prior to death. There was no significant regression of the tumor.

Final clinical diagnosis: Lymphosarcoma of the mediastinum.

At autopsy an anaplastic carcinoma originating in the right upper lobe bronchus was found.

Jaffé [8] reviewed 100 autopsied cases of primary carcinoma of the lung seen at the Cook County Hospital during a six year period. During the first three year period 47.5 per cent were misdiagnosed. During the second three year period after misdiagnosed cases of bronchogenic carcinoma were presented repeatedly at clinical-pathological conferences, the percentage of misdiagnosed cases dropped to 30 per cent. Other diagnoses made in Jaffé's series were:

Carcinoma of stomach, nine cases (stomach wall had been invaded in six cases).

Tuberculosis, nine cases (five had tubercle bacilli in the sputum).

Lung abscess, three cases.

Decompensated heart, one case.

Brain tumor or central nervous system lues, six cases.

Sarcoma of bone, one case (sternal metastasis).

Carcinoma of breast, one case (breast metastasis).

Carcinoma of prostate, two cases.

It is of the utmost importance to the neurosurgeon that he be aware of the frequency with which apparent primary central nervous system tumors prove to be metastases from bronchogenic carcinoma. In Fried's [1] group of 49 cases of bronchogenic carcinoma, 16 showed metastases to the brain. "12 of these were admitted to the service of Dr. Harvey Cushing with the diagnosis of a tumor of the brain." Ten were operated upon.

King and Ford,[11] in a clinical and autopsy study of 100 cases of bronchogenic carcinoma, found metastatic deposits in the central nervous system in 27. They concluded that a careful roentgenographic study of the chest is necessary in all cases of suspected intracranial or spinal cord neoplasms and in all cases of unexplained stupor.

In the present series cerebral metastases were found at autopsy in seven cases. In two of these cases the initial symptoms, headaches and convulsions in one and gradual hemiparesis in the other, pointed to a primary brain tumor. Roentgenographic study of the chest revealed the true primary site in both cases.

The diagnosis of bronchogenic carcinoma should be suspected in the presence of any one or more of the following symptoms: Cough, sputum, chest pain or discomfort, weakness, hemoptysis or blood-streaked sputum, loss of weight, dyspnea, wheezing or hoarseness. However, in analyzing the present data, an amazing variation was found in the pattern of the presenting symptoms (table 8).

TABLE VIII

Presenting Symptoms or Syndrome

1. Due to pulmonary involvement	24	
a. Cough, hemoptysis, chest pain, weight loss, repeated respiratory infections		18
b. Chest pain alone		2
c. Weight loss alone		2
d. Hoarseness, vocal cord paralysis		1
e. Pneumonia		1
2. Due to bone metastasis	7	
a. Low back pain (lumbar vertebrae)		5
b. Sudden loss of power, left arm (cervical vert.)		1
c. Bony swelling, right groin (ilium)		1
3. Due to brain metastasis	2	
a. Gradual hemiparesis		1
b. Headaches and convulsions		1
4. Due to other metastases	2	
a. To rectum (rectal mass)		1
b. To cervical nodes (neck mass)		1
5. Coincidental constipation	1	
Total	36	

Other unusual modes of onset, such as dysphagia, thrombosis of the superior vena cava by a compressing mass and jaundice produced by extrinsic occlusion of the common bile duct, have been reported.[8] It is probable that slight cough or minimal dyspnea occurred more frequently as an early but disregarded symptom. Our society, secure in the universality of the "cigarette cough," grows suspicious too late.

TABLE IX

Methods of Obtaining Tissue for Diagnosis

		+	−	0*
1. Pleural fluid		5	6	25
2. Sputum		0	7	29
3. Bronchoscopic biopsy		10	16	10
4. Direct aspiration biopsy		2	3	31
5. Lymph node biopsy		8		
Axillary	3			
Supraclavicular	2			
Inguinal	2			
Cervical	1			
6. Subcutaneous nodules		4		
7. Thoracotomy		2		
8. Aspiration biopsy of liver		1		
9. Bone biopsy, ilium		1		

* Key: + Positive for malignant cells.
− Negative for malignant cells.
0 Not done.

In the last analysis the diagnosis of bronchogenic carcinoma can be established only by the microscopic examination of an adequate biopsy specimen. In early cases the specimen is obtained either at bronchoscopy or at thoracotomy. In later stages subcutaneous nodules or involved lymph nodes can be biopsied. Pleural fluid may contain cells whose appearance is suggestive of malignancy. Sputum is rarely examined and almost never shows malignant cells when studied by older technics. However, aspiration of bron-

chial secretions at bronchoscopy and staining by Papanicolaou's method is a procedure which should be performed more often.

The following table lists the results obtained in the present series by the various methods of obtaining tissue. Thirty-three biopsies positive for malignancy were obtained in 25 patients. In 11 patients no histological proof of malignancy was obtained ante mortem. Eight of these cases died prior to 1939 when bronchoscopy was not employed routinely in every suspicious case (table 9).

Metastasis

Bronchogenic carcinoma spreads by direct extension, by extension to regional lymph nodes along peribronchial and perivascular lymphatics and by vascular invasion. Rarely growth along the bronchial mucosa is seen.

Most vascular invasion is venous invasion. When a malignancy at any other site invades a vein, tumor emboli are carried in the systemic circulation to the capillaries of the lung, or in the portal circulation to the sinusoids of the liver, where the tumor emboli are filtered out, grow and produce metastases. When a malignancy primary in the lung invades a vein, tumor emboli are carried to the left auricle and thence to any part of the body. It is for this reason that the appearance of metastases in bizarre locations such as the chin or thumb is characteristic of bronchogenic carcinoma rather than of malignancy primary in any other site. The various types of trophocarcinoma which metastasize in a similar manner seem to have an almost specific affinity for blood vessels.

The following table, showing the frequency with which metastases occur in multiple vital organs, summarizes the experience of several authors.

Table X

Metastasis in Bronchogenic Carcinoma

To	Jaffe[9] 100 Autopsied Cases	Ochsner and DeBakey[34] 3047 Collected Autopsies	Perrone and Levinson[35] 38 Autopsied Cases	Present Series 36 Autopsied Cases
Thoracic lymph nodes	89%	72.2%	*	47.6%
Other lung	43	23.3	20.8%	36.4
Adrenals	42	20.3	10.4	44.8
Abdominal lymph nodes	37		20.8	14.0
Liver	36	33.3	33.8	47.6
Kidneys	28	17.5	15.6	33.6
Bones	22	21.3	5.2	39.2
Brain	19	16.5	2.6	19.6
Intestines	8	4.3		8.4
Heart	7	12.7†	13.0	5.6
Pancreas	6	7.3	13.0	11.2
Spleen	5	3.5	7.8	5.6
Peritoneum	4	4.8		5.6
Skin	2	3.6	15.6	11.2
Pericardium	2		26.0	14.0
Pleura		29.8	31.6	22.4

* Peribronchial nodes 57.2%.
Mediastinal nodes 33.8%.
† Including pericardium.

Metastases were reported in occasional cases in the dura mater of the spinal cord, in thyroid, skeletal muscles, stomach, tongue, ovary, testis, breast, tonsil, diaphragm, aorta, esophagus, trachea, gall-bladder, etc.

Figures for brain and bone metastases are invariably too low because in many cases consent cannot be obtained for removing the brain and because a routine systematic examination of the bones cannot be made. In the present series bone metastases were found in 19 patients (53 per cent) during antemortem roentgen examinations. The findings were corroborated in 14 (40 per cent) of these patients at necropsy. The pelvis, femora and vertebrae were the common sites of unproved roentgen findings.

TABLE XI

Distribution of Bone Metastases

Bone Involved:	At Necropsy	On X-Ray
Vertebrae	6	9
Ribs	5	3
Pelvis	3	8
Femur	1	4
Scapula	1	1
Sella turcica	2	1
Radius	1	1
Ulna	1	2
Humerus	1	1
Sternum	1	1

The necropsy finding of bone metastases in 40 per cent is almost twice the usually reported incidence. It is probable that complete roentgen studies will disclose bone metastases in well over 50 per cent of all cases of bronchogenic carcinoma. The discovery by roentgen examination of a solitary lytic bone metastasis should suggest the bronchus as the possible primary site, especially in men over the age of 40.

TREATMENT AND PROGNOSIS

Bronchogenic carcinoma runs a rapid course. Both the mean and the median life expectancy in this series were only eight months from the onset of symptoms to death. No patient lived longer than 28 months after the appearance of symptoms.

TABLE XII

Duration of Life from Onset of Initial Symptoms

Number of Months	Number of Cases
0–3	4
4–6	6
7–9	9
10–12	5
13–15	4
16–18	3
19 and over	5

It might be noted parenthetically, that it is most difficult to determine the exact time of onset of symptoms truly referable to bronchogenic car-

cinoma. Not uncommonly initial minimal symptoms are overlooked, thus hastening the statistical course of the disease. On the other hand there are cases reported living as long as 240 months from the onset of symptoms, but without the slightest proof that these symptoms were caused by cancer.

When trained thoracic surgeons are available and when there is no discoverable evidence of metastasis, the earliest possible surgical intervention is imperative. Interval roentgen study of a suspicious pulmonary mass or hilar enlargement dooms the resectable case. Adams [9] who probably saw a higher percentage of early cases than are seen at the average general hospital, was able to resect only 49 of 157 cases. At the time of the report only 14, a bare 9 per cent, were living and well.

If the case is not curable surgically by pneumonectomy it is not curable. Bloch and Bogardus [17] reached the same conclusion in 1940 that Graham [16] had reached in 1936, namely, that "Up to the present (1940) irradiation has not been able to cure bronchogenic carcinoma." More encouraging results have been reported by Hocker and Guttman [26] with the 1,000 kilovolt roentgen therapy unit. These early results await the test of time.

Has roentgen therapy any place in the treatment of bronchogenic carcinoma? Most careful studies answer that question affirmatively.[18, 19, 20, 21, 26] If given before the patient has reached a preterminal state an average increase in life expectancy of about six months results. Of perhaps greater importance to the patient is the relief of pain, diminution of cough and hemoptysis, improvement in appetite and gain in weight that not infrequently follow roentgen therapy. The improvement is occasionally spectacular. One patient under observation at present (V. S.) has gained more than 20 pounds in weight during and after a course of radiation therapy. There has been no coincident roentgen evidence of improvement.

In many cases roentgen therapy produces absolutely no improvement. It is not possible to predict improvement on the basis of the microscopic cellular character of the biopsy specimen. Anaplastic carcinomas are usually regarded as the most radiosensitive. Yet Steiner [22] felt that "Squamous-cell carcinomas and adenocarcinomas of the lung were more radiosensitive than were the undifferentiated carcinomas which, contrary to their microscopic appearance, were either highly radioresistant or highly radiorecuperative."

Before metastases have become widespread the aim of roentgen therapy should be to administer as large a tumor dose as can be given within the limits of skin and physical tolerance. The smallest tumor dose which has been shown to produce visible histologic damage is 1,490 r.* The carcinocidal dose is probably above 5,000 r.[22]

The following case received a tumor dose of 3,840 r with complete disappearance of a bronchoscopically visualized and biopsied anaplastic carcinoma. Death, caused by generalized metastases, occurred nine months after the appearance of the initial symptoms.

* Roentgen unit.

C. K., a white male 61 years of age, was admitted to another hospital on May 13, 1940 because of a "heavy cold" and persistent productive cough of two months' duration. On physical and roentgen examination a large left pleural effusion was discovered. A chest tap was productive of bloody fluid containing cells irregular in size, shape and staining quality and strongly suggestive of malignancy. On June 11, 1940 he was referred to the Brooklyn Cancer Institute for radiation therapy.

The above findings were corroborated and, in addition, bronchoscopy revealed a mass in the left main bronchus. The biopsy report was anaplastic carcinoma. On June 29, 1940 deep roentgen-ray therapy was begun to one anterior and one posterior left upper thoracic port, 10 × 15 cm., 200 Kv., 1.8 mm. cu. Hvl., 50 cm. T S D, 200 r to two ports daily to 4,000 r in air per port. The total tumor dose was 3,840 r. Therapy was completed on August 1, 1940. Four days later a chest roentgenogram confirmed the physical findings of disappearance of the pleural effusion. No definite mass could be seen in the left lung field. On September 19, 1940 the patient was readmitted because of chest pain, weakness and progressive emaciation. Roentgenograms of the chest at this time showed only slightly increased pulmonary markings in the left lung field. Bronchoscopy on October 8, 1940 revealed that the previously-noted mass in the left main bronchus had disappeared. On November 5, 1940 numerous small hard subcutaneous nodules were noted in the abdominal wall. One of these nodules was biopsied and reported to be metastatic anaplastic carcinoma identical in all respects with the bronchoscopic biopsy of June 27, 1940. The patient grew weaker and died on December 12, 1940, nine months after the appearance of the initial symptoms.

TABLE XIII

Patients Surviving 15 Months or More

Name and Hosp. No.	Survival After Onset of Initial Symptoms (Months)	Tumor Dose (Roentgens)	Comment
A. G. (6)	15	3600	Marked clearing of atelectasis
J. D. (165)	15	7500	Great clearing of left upper lobe atelectasis
J. D. (4074)	15	1800	No effect of radiation
H. U. (4080)	16	2800	No effect
B. B. (4120)	16	none	Antemortem diagnosis—adenocarcinoma of rectum
E. T. (3743)	17	none	Patient seen terminally
E. D. (7609)	19	none	Pneumonectomy
O. Z. (6121)	20	2000	No effect
G. S. (3199)	20	2600	1st course,
		3200	2nd course, no roentgen changes but marked clinical improvement and weight gain
F. M. (1762)	23	none	Patient seen terminally
P. K. (6944)	28	1400	No effect

At necropsy numerous metastases to subcutaneous tissue, pancreas, adrenals and liver were found. The left main bronchus was studied with the utmost care. "An area roughly 3 cm. in length which involves the terminal portion of the left main bronchus and the proximal portions of both upper and lower lobe bronchi is distinctly different in appearance from the remainder of the bronchial tree. The lining appears shiny and atrophic." On microscopic examination "the mucosa is thinner than normal. Only an occasional recognizable lining epithelial cell is present. Submucous tissue is decreased in amount. There is a scant infiltrate of lymphocytes and plasma cells. One of the larger arteries shows marked subintimal thickening. No tumor cells are present."

In this small series there were 11 patients who lived 15 or more months after the onset of symptoms. In this group there was no relation whatsoever between the tumor dose administered and longevity. Three of these patients received tumor doses of 3,600 r or more. Two showed marked clearing of atelectasis; one showed no roentgen changes but gained weight and manifested considerable clinical improvement (table 13).

Many of the 25 patients who lived less than 15 months after the onset of symptoms did not live long enough to receive a significant amount of roentgen therapy. In four cases, however, tumor doses of 3,000, 3,300, 4,000, and 3,800 r were given with survivals of only six, six, eight and eight months respectively. Only the fourth of these cases showed any effect of radiation that could be measured objectively—complete disappearance of the primary tumor (Case C. K. above).

Conclusions

The rising incidence of bronchogenic carcinoma together with the possibility of surgical cure by pneumonectomy, demands the earliest possible diagnosis.

Bronchogenic carcinoma may soon rank first among malignancies causing death in the male.

The diagnosis of bronchogenic carcinoma must be considered in any individual past 30 years of age with symptoms or signs referable to the chest, with low back pain, with suspected cord or brain tumor or with bizarrely located metastases.

Roentgenographic study of the chest should suggest the proper diagnosis relatively early in about 60 to 75 per cent of cases of bronchogenic carcinoma.

Routine early bronchoscopy in every suspicious clinical syndrome is vital to early diagnosis and will increase the percentage of biopsy proved cases.

In many cases a major portion of the clinical course is characterized by evidence of serious pulmonary suppuration—fever, leukocytosis, anemia—whose presence should not be felt to render the diagnosis of bronchogenic carcinoma less likely.

The average life expectancy at the present time is only eight months from the onset of symptoms to death.

Demonstrable bone metastases can be found by careful roentgen study in more than 50 per cent of cases.

Every case without metastases or evidence of local invasion of vital structures should have the benefit of an exploratory thoracotomy.

Roentgen therapy although merely palliative with the generally available 200 kilovolt apparatus, should be given as early as possible after the determination of non-resectability.

Tumor doses above 5,000 roentgens should be administered if maximum benefit is to be derived.

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PSYCHOSOMATIC ASPECTS OF CARDIAC ARRHYTHMIAS: A PHYSIOLOGICAL DYNAMIC APPROACH *

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THE expression of emotional reactions in bodily function has been recognized and appreciated by both layman and physician since antiquity. Where the relationship between the functional disturbance and emotional upset is external, it is easily recognized and becomes amenable to treatment. However, where the disturbance is deeply rooted in the psyche, the diagnosis of the physical disorder may remain obscure and the condition then becomes resistant to the ordinary forms of therapy. Certain nosologic entities, such as peptic ulcer, mucous colitis, Graves' disease and hypertension, which a few decades ago were considered essentially somatic in origin, have been shown to be manifestations (at least in part) of a disorganized personality and often are effectively treated through psychotherapy. It is considered that in such patients pent-up energies which have failed to find proper external release develop tensions which tend to localize themselves in various organ systems, alter their natural functional capacity, and thus give expression to apparent somatic disease.

The heart is one of the most sensitive targets for stimuli of psychic origin. When such stimuli impinge frequently and over a period of time, the normal heart becomes increasingly sensitive to the slightest emotional stress, ultimately reaching a point where the individual may be continually conscious of some apparent cardiac defect. On the other hand, organic heart disease often produces emotional disturbance by creating situations of constant worry, preoccupation, and fear. Cardiac arrhythmias of any genesis may lead to dizziness, syncope, headaches and anxiety states. The interplay between the cardiovascular apparatus and the emotions is an intricate, two-way affair and it is understandable that, on occasions, the primary mechanism in the vicious cycle may be hard to determine.

Neurotic behavior accompanied by somatic complaints referable to the heart or cardiac fixation without somatic symptoms has been classified as "cardiac neurosis." It has as its central theme anxiety and fear, and is, in all likelihood, a special type of anxiety neurosis. The precipitating factors for the cardiophobia in an individual with neurotic tendencies are numerous. For instance, the unexpected death of a parent has often been responsible for

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inducing anxiety and fear of a similar fate, since in the mind of the layman, heart disease is a hereditary condition. The patient in this group may not complain necessarily of any particular symptoms, but may be worried as to "how long his heart will last." Where chest disturbances are present, whether of the thoracic cage itself or of any organ within the thorax other than the heart, the symptoms are interpreted by the patient as those arising from a diseased heart. In this group of patients careful investigation has failed to reveal any organic basis for their cardiovascular disturbances. Inquiry into the character and site of chest pain, which is a common complaint, will disclose it to be located in the apical region or left side of the thorax and characterized by protracted twinges of darting pain or of a burning sensation unrelated to physical effort. Such symptoms are characteristically different in genesis, location, and distribution from pain engendered by organic cardiac disease.

Cardiac irregularities may occur during or following an emotional episode. The patient may complain of conscious heart action, or in extreme cases, of his heart "jumping out of his throat," dizziness, and even unconsciousness. In the sensitive individual premature systoles may be very disturbing. This is well illustrated by the personal experience described by Reinhardt [8]: "The extrasystole has always affected me as if it were a cannon ball shot point-blank at my brain. The sensation is that of a terrific explosion occurring within the narrow and limited confines of a calcified skull, which refuses to yield to the compressive force. It is like an irresistible force against an immovable object. Most of the time I am helpless before it, and simply wait patiently in terror until the ordeal has passed. I have never been able to satisfy myself as to why I never suffered the sequelae of a cerebral accident following an extrasystole, for I can think of no other sensation which can so closely simulate breaking of a blood vessel in the brain without doing so."

It is a common experience that a neurosis developing in the course of organic heart disease or during convalescence from acute heart disease adds a definite physiological load upon the already overburdened heart. Thus, it becomes apparent that the emotional aspects of heart disease, aside from the effect of emotion upon the otherwise normal heart, are important considerations which the physician must face in outlining adequate therapy.

Attempts have been made in numerous psychiatric studies to formulate a personality pattern of patients whose chief complaints are of the disabling effects of a disturbed cardiac rhythm.[2] While there is merit in methods attempting to develop the personality profile of these patients, it still is best to consider such efforts as first approximations which future studies will have to define more clearly. The personality pattern has been described as follows: While these patients in many instances show marked similarity to other groups of cardiac patients, there is usually a higher incidence of familial cardiovascular disease and neurotic trends in other members of the

family. They give a history of frequent illness, either of cardiac origin or following accidents, and they have been exposed since childhood to life situations of anxiety, fear, and overindulgence by the parents. They are extremely sensitive to criticism, to which they react with a sense of impotence and repressed hostility, retreat and find release in their illness. Once their hostility is aroused, however, they react with vehemence, and when the emotion is spent, try to elicit sympathy on the basis of their cardiac condition.

The influence of emotion on the cardiac rhythm and the effects of this disturbance on the emotional life of an individual are exemplified by the following case report:

A 50-year-old white female was first seen in 1939, in the Out-Patient Department, complaining of bouts of palpitation occurring with exertion or at rest, and occasionally during sleep. These episodes would last for several hours and at times were accompanied by a sense of sternal oppression, dyspnea, fullness in the head, and by a terrifying feeling that blood was about to gush from her nostrils. She often had the impression of impending death either by hemorrhage or cardiac rupture. Between attacks there were few, if any, symptoms to indicate the presence of cardiovascular disease. There was no dyspnea on walking on flat ground and only moderate breathlessness on climbing stairs. She had no peripheral edema nor undue fatigue after a heavy day's work. Other chest discomforts, which occurred more often than the major attacks of palpitation appeared, were in the form of fleeting twinges of pain. Her other complaints were intolerance to fatty or dried foods, which, when taken, were usually accompanied by a sense of fullness and upper abdominal distress. She had these symptoms for many years prior to and after undergoing a cholecystectomy in 1935.

Physical examination revealed a well-composed, well orientated woman of average intelligence, with few positive physical findings. The cardiovascular system presented no abnormalities. The size of the heart was normal. The heart sounds were clear, regular and of good quality; the rate, 60 beats per minute; there were no murmurs; the blood pressure was 130 mm. of mercury systolic and 70 diastolic. There were no signs of peripheral vascular disease. The lungs were clear. The only abnormality in the electrocardiogram was a slight depression of S–T in Lead I, which was objectively considered as one indicating minimal, if any, damage of the heart. The roentgen-ray examination of the chest substantiated the physical findings of a normal heart and lungs. Serologic tests for syphilis were negative. Blood studies revealed a moderate hypochromic anemia; hemoglobin, 70 per cent, and the red blood cells numbered 4.4 million per cu. mm. The white count was 7.4 thousand per cu. mm., with a normal differential. The urine was negative. Sedimentation rate was 15 mm. in one hour. Fasting blood sugar was 71 mg. per cent, and the non-protein nitrogen was 35 mg. per 100 c.c. of blood. Repeated fasting blood sugars were within normal range in spite of the patient's insistence that she had been diagnosed a diabetic on various occasions.

The only significant positive finding was a high basal metabolic rate. This was repeated on numerous occasions and varied from plus 9 to plus 34 per cent. There were, however, no clinical signs, symptoms or other laboratory tests substantiating the possibility of hyperthyroidism. On the basis of her symptoms, a diagnosis of paroxysmal tachycardia (probably supraventricular) was made. The treatment consisted essentially of reassurance and sedation.

Course: During the ensuing six years, the patient was observed and treated by a number of physicians in the Cardiac Clinic on various occasions, without apparent relief of her symptoms. At times, she was given nitroglycerine to relieve the chest

pain, but this was without obvious effect. At other times, she was placed on therapeutic doses of digitalis, again without apparent benefit. The attacks of spontaneous palpitation became increasingly more frequent and lasted for longer periods. She was finally admitted to the Hospital in April, 1944, with a number of new and striking symptoms. She now complained of frequent vomiting, nocturia, pain in the legs, and acral paresthesia. Her dyspnea and chest pain were, in her estimation, definitely worse. Now the chest pains lasted all day and only on rare occasions were they relieved by nitroglycerine. The pain had no constant location in the chest, and, when occurring, would often radiate down to the abdomen and initiate vomiting. Regurgitation of food accompanied by a sour taste occurred after almost every meal. Again, physical examination and extensive laboratory work-up revealed no organic disease to account for her symptoms. Her basal metabolic rate on one occasion in the hospital was minus 4.7, and on another, was plus 15.7. Serial electrocardiograms showed no change from that seen six years previously. While at the hospital, all of her symptoms disappeared following mild sedation. She was discharged after remaining in the hospital for several weeks, and again was reassured as to the benign nature of her condition.

Several months later her cardiovascular symptoms reappeared. However, each time that she was examined in the clinic, the heart rate ranged from 60 to 80 beats per minute and repeated electrocardiograms failed to show any change. Finally, in February, 1946, she was re-admitted to the hospital for operation of a hallux valgus and for further investigation of her cardiac complaints. While at the hospital during preparation for this operation, she developed severe palpitation, with marked substernal oppression and symptoms of mild shock. Her pulse rate was 180, regular, and of poor quality. Her blood pressure was 180 systolic and 100 diastolic. Because of the possibility of acute myocardial infarction with a paroxysmal auricular flutter, an electrocardiogram was taken immediately and it revealed a paroxysmal auricular tachycardia. The mechanism was broken by the oral administration of 6 grains of quinidine, given every two hours. Serial electrocardiograms taken after this attack revealed a normal sinus rhythm with a rate of 80 beats per minute, without evidence of a recent infarction. She was operated upon several days later and had an uneventful recovery.

Life Situation: The patient, the third in a family of five, was born in Poland into an orthodox Jewish family. Her father was a good provider and managed to maintain a harmonious home life. Throughout her childhood, the patient felt closer to her father than to her mother, and respected his ideas on all her personal problems. At the age 20 years, her father arranged a marriage for her with a man many years her senior (to this day, the husband refuses to tell her his correct age). In spite of the fact that she had seen the groom only on two different occasions, she married him at the insistence of her father. Her husband, a tailor by trade, was a hard, conscientious worker, but managed to earn only enough to meet the bare necessities of living. One year after her marriage she delivered her first child. Since the family income was very meager at this time, her husband decided to leave for Chicago with better financial prospects in view. This was planned with the understanding that she meet him there at a later date. The patient took the opportunity of her husband's departure to seek a separation, but again, pressure from her father forced her to leave Poland and rejoin her husband. As in Europe, her husband's income was small, but the patient now decided to make the best of it. She became pregnant a second time, but a spontaneous miscarriage occurred. A third pregnancy followed, with the birth of a girl. Throughout her married life up to this point, her father continued giving her wise counsel by mail. She, in turn, conscious of her obligations as a mother and wife, decided to make the best of the family resources. In her own words, "I never loved my husband, although he loved me very much. Because he was a hard worker,

didn't spend money on drinking or smoking, and tried to make a living, poor as it was, for his family, I would not desert him." She shed all her love on her children and was closely associated with their personal problems. Minor illnesses up to this stage of her life were inconsequential. Then her daughter, at the age of four years, developed rheumatic fever; this was followed by repeated attacks, the child finally dying at the age of eight years. The emotional blow was so great to her that, "even today, I can't forget her." After this episode, she became more irritable and could be easily agitated by minor difficulties.

Twelve years ago, a significant event occurred in her life. While shopping, a woman standing close to her picked her pocket of $10. Upon discovering her loss, she appealed to the manager of the store to search the woman, but he refused and reprimanded her for false accusation. That night, on returning home, she was extremely upset, depressed, worried and anxious in regard to the effect this would have on the family economy. While preparing for bed that night, she suddenly experienced severe palpitations, faintness, and she collapsed. A physician, called in to see her, diagnosed the condition as a heart attack and kept her confined to bed for two weeks. After this episode, the patient observed that any anxiety or frustration was followed by palpitation and substernal discomfort. The next "great shock" occurred five years later, when she discovered that her son, to whom she was very closely attached, had been secretly married to a girl of whom she heartily disapproved. In the patient's own words, "This girl was a well-educated person, but always sick. Every time my son brought her over, they had to leave to keep an appointment with a doctor. I think she had pelvic trouble from an abortion. I tried hard to break it up, but he married her in spite of my wishes. I have no use for my daughter-in-law; she visited me for a few minutes while I was in the hospital. I dislike her because she has taken my son's affection away from me." The complaints of palpitation, substernal discomfort, and nocturia occurred frequently, and would appear even when she was not consciously under stress. The patient felt that she could never honestly express her troubles to her friends and get worthwhile advice, so she kept them hidden within herself "to a point of bursting." She resigned herself to her lot in life and sincerely believed that she had enough insight into her difficult situations to enable her to manage them herself.

Dream Material: One significant dream, still vivid in the patient's memory, occurred during the pregnancy of her second child. "My father came into my dreams and told me that he was dead. He asked me to name the child after him and never to leave my husband." The next morning, she asked her husband whether he had received any letter telling of her father's death. Her husband denied such knowledge, but several weeks later, a letter from her mother informed her of her father's death. The dream had made an indelible impression upon her for the rest of her life.

Comments: This case clearly illustrates the problems which beset physicians trying to integrate somatic disturbances with emotional maladjustment. While physicians, regardless of background, admit the general proposition of the interplay between emotion and organ function, there is a divergence of opinion in the application to particular circumstances. The approach to the entire problem and the interpretation of the mechanisms and etiologies involved vary widely, and to a large extent depend upon the previous background of training of the physician concerned. There is need for a common meeting ground, and it can only be hoped that by the slow and painful process of evolution, this will eventually come about. Until this objective is reached, one can expect considerable overswing and apparent conflicts of opinion.

To be concrete, the physician who, after thoroughly examining the patient and finding no physical basis for his complaint, dismisses the case as one of organ neurosis, "functional," or as an "irritable organ," may overlook an important aspect. Such a diagnosis should not be made simply by the exclusion of organic findings. A very important factor in diagnosing organ neurosis is the securing of positive psychological evidence of the existence of a disturbed emotional state. This is just as important as the finding of positive roentgen-ray evidence for the diagnosis of a peptic ulcer. The psychiatrist sees the patient as one with pent-up anxieties, frustrations or suppressed hostilities which express themselves in disturbed organ function. Perhaps he has worked out personality patterns which, when noted in a patient, signify that sooner or later the patient will succumb to a particular functional disturbance.

The physiologist points to the fundamental investigations of Pavlov on conditioned reflexes and shows that the so-called organ neurosis may be interpreted as a form of conditioned reflex. Thus, it has been demonstrated that dogs, conditioned to secrete saliva in response to a given stimulus, lose this ability when the stimulus becomes one which induces fear. The physiologist, furthermore, can point to the more generalized studies of Cannon and his associates, who, starting with this fundamental concept, have elaborated the manner in which fear, anger, and the like disturb the normal economy of the human body.

Under normal physiological conditions, there is a constant dynamic fluctuation in the function of the organism as an expression of its adaptive capacity to its environment or to the immediate internal demands of one organ system upon the others. This ability to adjust and to maintain a homeostatic equilibrium is achieved in two ways: namely, (1) by the function of the autonomic nervous system, and (2) by humoral mechanisms initiated by the endocrine system. The humoral and autonomic mechanisms are not independent but interdependent in modifying specific organ activity. The older view that either the sympathetic or parasympathetic system is predominately active in personality disorders, and the consequent labelling of the patient's condition as a functional disorder of sympathetic or vagotonic origin, is too rigid a concept. Patients may show manifestations at one time suggesting sympathetic and at other times, parasympathetic dominance.

Probably a more dynamic view is that both nervous systems are called into play in the same emotional situation; the character and intensity of the emotional stimulus and the variation in the tonic state of the two parts of the autonomic nervous system determine the dominance of one system over the other for that particular circumstance. Recent studies [12] in our laboratory serve to illustrate the effect of autonomic influence on ectopic rhythm; thus, paroxysmal ventricular tachycardia produced by intravenously injected adrenalin was abolished by the administration of atropine, without affecting the concomitant paroxysmal hypertension. While the differentiation of

sympathetic and parasympathetic effects can be fairly sharply demonstrated in animal studies, in neurotic behavior, on the other hand, one does not ordinarily deal with so simple a pattern. One would, therefore, not expect a specific sympathetic or parasympathetic response, but rather, one of composite character producing varying responses in the same individual on different occasions.

The summation of psychic stimuli, regardless of its pattern, must exert its effect through either one or the other subdivision of the autonomic nervous system, with modification by direct and indirect influence on the endocrine glands. These facts are applicable to disturbances in cardiac rhythm and must be accounted for in the consideration of the effect of emotional disturbances upon the beating of the heart. The direction that emotional release will take via the autonomic nervous system depends upon the path of least resistance in the organism, determined, so it would seem, by the personality profile developments since infancy. Rational analysis would, therefore, indicate that the approach to the psychosomatic problem is to blend all of these views into one general concept based on the premise of the indivisibility of psyche and soma.

The human heart, by virtue of its inherent pacemaker, is capable of rhythmic contractions when removed from the body (as has been shown in isolated hearts removed from executed criminals); nevertheless, in vivo it is under the constant influence of the central nervous system with centers located in the medulla oblongata in the floor of the fourth ventricle.[11] These centers are tonically active; that is, they exert their influence constantly. They consist of an inhibitory and augmentory center lying in close proximity and, due to their delicately balanced state, regulating the activity of the heart and vascular system in a smooth fashion. Their balance is adjusted to the homeostatic needs of the body. This is brought about by the impingement of impulses via afferent nerves arising from end organs of special and general sensation in somatic structures, especially from those located in the lungs, heart, and blood vessels. The most important of these visceral groups of end organs are located in the root of the aorta and in the carotid sinus. The various impulses which the cardioregulatory centers receive from these organs produce continuous reciprocal changes in the tonic balance of the two parts. Thus, while causing a depression in the tone of one, they produce a simultaneous increase in the tone of the other.

The cardioregulatory centers are influenced by impulses arising from the hypothalamus and cortex. However, there has been no clear-cut evidence that any voluntary control of the heart activity can occur. One of the rôles of these higher centers appears to be associated with automatic adjustments accompanying voluntary and involuntary activity which may result from emotional disturbances. It has been shown experimentally that cortical stimulation influences the cardioregulatory centers. Thus, faradic stimulation of the cortex adjacent to the precentral sulcus evokes pronounced

alterations in the heart rate, among other cardiovascular responses.[4] It is significant that these areas influencing cardiac activity are in close proximity to those of somatic function. As Fulton [3] has stated, "The newer disclosures concerning the cerebral cortex and the autonomic nervous system give an adequate physiological basis for the long recognized relationship between mental states and visceral processes." It is this influence of the higher centers on autonomic function and the effect of disturbed somatic functions on these centers with which psychosomatic medicine is particularly concerned.

Recent experimental work has shown that autonomic nervous regulation of the heart, as well as of blood pressure and many metabolic functions, is under the control of centers situated in the hypothalamus. Stimulation of the anterior hypothalamus produces slowing of the heart rate and prolongs A–V conduction. Stimulation of the posterior hypothalamus causes tachycardia and frequent premature systoles.[1] Such experimental observations are strongly suggestive of the existence of subcortical centers influencing cardiac activity. In addition, there is reason to believe that these hypothalamic centers are related to emotional expressions and that they may operate either directly upon the cardioregulatory centers or indirectly through their influence upon endocrine activities.[7]

Psychic impulses may, by upsetting the tonic balance in the cardioregulatory centers, cause: (1) depression or stimulation of the primary pacemaker of the heart, producing sinus tachycardia, sinus bradycardia, and sinus standstill; (2) increased irritability of subsidiary pacemakers, giving rise to paroxysmal tachycardia of supraventricular or ventricular origin or to paroxysmal auricular fibrillation and flutter, and even possibly to ventricular fibrillation with sudden death; and (3) heart block, i.e., S–A or A–V block, and more rarely, intraventricular block. The case given in detail above is an example of paroxysmal tachycardia initiated by an emotional episode. A case presented by Wedd et al.[10] illustrates the influence of emotional disturbances in producing S–A block in a patient with mitral stenosis.

From this brief consideration of the intricate nervous control of the heart beat, one can appreciate the wide range of influence that psychic disturbances may have in deranging the normal rhythm of the heart. The relay of activities, starting from the initiation of a psychic impulse originating in the higher brain centers to the first appearance of a disorganized heart beat, is intricate and far from being well understood. While it has been shown experimentally that the cortex, hypothalamus, the cardioregulatory centers, and endocrine systems can, when stimulated individually, cause a disturbance in cardiac mechanism, yet their coördinate activity and the relative importance of each of their rôles in carrying out this event have not, as yet, been precisely determined. It has been mentioned previously that areas have been located in the cortex which are concerned with cardiac regulation. Likewise, the hypothalamus has been demonstrated to influence cardiac

activity either through its nervous connections with the cardioregulatory centers or by its direct sympathetic connections with the cardiac plexus.[1] Furthermore, the hypothalamus may affect cardiac mechanism through its influence on the endocrine system, particularly on the thyroid and adrenal glands.[7]

The endocrine system plays a relatively important rôle in the homeostatic regulation of cardiac function.[13] The influence of the hormones is brought into the foreground whenever a hormonal imbalance is present in the body. Clinical and experimental observations with oral and parenteral administration of hormones have, in many instances, clarified their precise action on the cardiac mechanism. Hormones may exert their influence directly upon the heart or may act through the medium of the autonomic nervous system. A dynamic interdependence exists between these two systems. For example, unilateral stimulation of the cervical sympathetic nerves causes an increase in thyroxin output from the corresponding half of the thyroid gland; on the other hand, hormones may sensitize the autonomic nervous system, as evidenced by parenteral injection of large doses of purified thyroid or sex hormone preparations. Thus, arrhythmias which are frequently encountered in patients who are treated for obesity with large doses of thyroid extract may be accounted for on this basis.

A few examples of arrhythmias encountered in various endocrine dyscrasias will emphasize the importance of the endocrine glands in causing cardiac irregularities. Thus, rapid heart action is frequently observed in hyperthyroidism. This may occur in the form of sinus tachycardia, transient auricular fibrillation or flutter. Hypoglycemia, either as a result of pancreatic overactivity or insulin overdosage, is attended by an increase in heart rate. Tumors of the adrenal cortex and medulla are frequently associated with tachycardia. Tachycardia is common in hypofunction of the sex glands associated with the menopause. Slow heart action occurs most commonly in hypothyroidism. Hyperpituitarism associated with pituitary tumors also leads to bradycardia. Premature systoles are frequently encountered in hypoglycemic states, in hyperthyroidism, and in hyperadrenalinism. A–V or intraventricular block occurs at times in hyperthyroidism and disappears after thyroidectomy.

It would thus appear from the evidence presented that cardiac arrhythmias can result from imbalance either of the autonomic nervous system or from imbalance of the endocrine system, and that these two systems are inter-related in rather complex ways. It is further evident that emotional disturbance can operate via the nervous system to set up imbalances in the autonomic and endocrine regulation of the cardiovascular system.

In order to elucidate further the clinical aspects of psychogenic cardiac arrhythmias, it is necessary to examine briefly certain clinical aspects of the more commonly occurring arrhythmias. Cardiac irregularities often are disturbing to the patient; they lead to unpleasant sensations, and there is

a tendency to regard them as invariably signifying a disturbance of heart action, with serious implications. This is true only in instances when the irregularity complicates existing serious heart disease or when the irregularity leads to prolonged and very rapid heart action in a normal heart. In either case, the abnormal rhythm imposes a load upon the cardiovascular system sufficiently great to lead to the possibility of coronary insufficiency or congestive heart failure. It is, therefore, essential to understand the origin and mechanism involved in the various arrhythmias in order to better appreciate their clinical significance.

Arrhythmias may arise as a result of (1) disturbance in discharge of the primary pacemaker; (2) defective conduction in various parts of the heart; or (3) ectopic rhythms arising from foci in the auricles or ventricles.[5]

Sinus arrhythmia per se seldom causes symptoms. When present, however, in neurotic patients with heart consciousness, it may lead to palpitation, dizziness, and fainting. Prognostically, it is unimportant in normal hearts. Sinus bradycardia, while ordinarily symptomless, may cause emotional disturbances sufficient to necessitate intervention when the slowing of the heart rate becomes either profound or markedly irregular. Sinus tachycardia may appear as palpitation, dizziness, or as an unpleasant sensation over the chest, often misinterpreted as angina pectoris. In persons with coronary insufficiency, its sudden development may tend to precipitate an anginal attack. While sinus tachycardia is a mechanism by which the heart can maintain an adequate flow of blood to the tissues, when excessive, it may actually set up a vicious mechanism contributing to the development of progressive heart failure in such patients.

Depending upon the type of individual, premature systoles may or may not cause symptoms. In patients under constant tension, their presence may induce alarming symptoms, such as has been quoted earlier. The patient may be conscious of a pause after the beat or he may experience the vigorous beat that follows. In mild instances, he may be conscious of the irregularity of his heart action; in extreme instances, he may complain of sudden fullness in the chest or head, choking, or chest pain. As in the case of sinus tachycardia, the unpleasant sensation may be misinterpreted as angina pectoris and it may contribute to a cardiac fixation, especially in apprehensive individuals. Since premature systoles are inefficient beats of the heart, their frequent occurrence imposes an extra load upon the cardiac apparatus. In this respect, they may contribute to the development of congestive heart failure and to coronary insufficiency in patients already suffering from organic heart disease. On the whole, the symptoms caused by premature systoles are more alarming than their potential ill effects would justify.

Supraventricular paroxysmal tachycardia occurs at any age and is found more often in the absence than in the presence of heart disease. The history of an attack is often quite characteristic. The patient may reveal that following a disagreeable thought, a period of emotional stress, or a sudden

movement of the body, rapid heart action began abruptly. Sometimes, the attacks occur during indigestion, fatigue, infections or thyrotoxicosis. The character and severity of symptoms following paroxysmal tachycardia of supraventricular origin depend upon the duration of the attack, the emotional health of the patient, and the presence of heart disease. Patients complain of palpitation, fluttering, pounding in the chest, dizziness, faintness, smothering oppression, or substernal pain. In appearance, the patient may be pale, gray, cyanotic, dyspneic, and in extreme cases, may become comatose and develop convulsive seizures. Such cases have been misdiagnosed as epilepsy. In the presence of organic heart disease, rapid heart action contributes to a downward course leading to congestive failure, and it may be the trigger mechanism involved in precipitating angina pectoris.

Auricular flutter and auricular fibrillation occur in a paroxysmal and a chronic form. The chronic types are nearly always associated with organic heart disease; the paroxysmal types, on the other hand, occur occasionally in hypersensitive individuals following intense emotional upsets. Sino-auricular block may occur both in diseased hearts [10] and in normal hearts [9] following psychic trauma.

Consciousness of heart action such as is apt to be produced by cardiac irregularities is all too frequently misconstrued by the average individual as real heart disease. This general misconception has been inadvertently abetted in recent years by the advent of radio health talks and newspaper articles, especially those tending to dramatize cases of sudden death. While it cannot be denied that these topics are generally informative and helpful to the laity, nevertheless, they open up new avenues of thought to the supersensitive individual, and by a process of suggestion, find fertile fields for elaboration in benign cardiac disorders. It is so easy for the uninitiated to fit signs and symptoms that they hear about into their own particular conditions and to imagine that they have serious heart disease. The cardiac death of a near relative or close friend, or even the acquaintance of a person ill with organic heart disease, often induces introspection with consequent anxiety and fear of a like fate. Similarly, a chance remark by a physician regarding the presence of a murmur, or of a premature systole, etc., to a patient whose personality makeup he has failed to assess properly, has often induced heart consciousness. Probably as notorious in this respect has been the rejection of an individual for life insurance, from the Armed Forces, or from industry because of some borderline cardiac arrhythmia which, in itself, is otherwise of no moment to the person concerned.

In psychoneurotic individuals, such situations are usually followed by anxiety and cardiac fixation, and almost invariably start him off on the usual rounds of physicians' offices. Digitalis prescribed indiscriminately by otherwise well-meaning physicians, has also shared considerably in inducing cardiac fixation. Among the laity, the administration of this drug connotes serious heart disease. The use of this agent in the treatment of

benign cardiac arrhythmias without careful explanation and assurance to the patient has, on occasion, led to irreparable cardiac invalidism.

These facts lead to the obvious deduction that the physician must take special care in obtaining a history and physical examination of such patients. A sympathetic attitude by the physician and encouragement of the patient to tell his story in his own way, while not productive of an orderly history, and while time-consuming to the busy practitioner, nevertheless, have much in their favor. They provide the means for the physician to assess the patient's personality makeup and give insight into the possible functional nature of the ailment. For the patient, these methods aid in developing confidence in the physician and set him up as a parent-ideal or substitute. Occasional interruptions and repetition of the more important statements tend to bring the idea of the benign and functional character of his complaints into the patient's conscious awareness. Ventilation of emotional conflicts often suggests to the patient their possible rôle in his present illness, and at times affords considerable psychotherapeutic benefit.

During the physical examination, the physician should be careful not to concentrate too long upon any particular region of the chest and not to appear perturbed about any physical finding that he encounters. Patients are anxious, always suspicious, and watch the physician most carefully. Training in the proper technic of performing a physical examination is as important as the scientific interpretation of the findings. Abnormal physical findings require a simple, adequate explanation of their mechanics, clarification of the significance of the emotional rôle, and assurance that the irregularity is, at most, a normal physiological variation occurring in healthy individuals. The positive physician, who is self-assured and leaves no doubt that his explanation is correct, is valuable to such a patient. The more hesitant physician, on the other hand, uncertain of the adequacy of his explanation, may actually do the patient considerable harm. These statements are especially applicable in the case of the sensitive individual, the one with easily upset emotional balance.

The confidence established in the physician by the patient, and his demonstrable interest in the patient's case, together with a complete cardiac examination and a simple explanation of the disturbance, is psychotherapy in its simplest form. A goodly percentage of patients respond to such management. In all instances, the chances of good psychotherapeutic results will depend upon the patient's inherent ability to deal with his emotional problems on the one hand and the flexibility of his life situation on the other. When the life situation does not allow for modification, and when the changes to be made depend upon the patient's capacity to adapt himself to his own environment, the treatment is long and progress becomes exceedingly slow. Removal of certain irritating factors from the patient's environment, or a complete change in surroundings yields considerable impetus towards re-

covery. This is often seen during the patient's vacation away from the strained environment of his home or office.

Cases are occasionally encountered in which psychosomatic symptoms have existed for years, have become progressively worse, and have interfered with the patient's routine of living. Such individuals have, with time, built up defenses too difficult to remove by ordinary procedures. They require careful psychoanalytic study and should be referred to the specialist.

Even though the arrhythmia has been diagnosed as psychosomatic, all aids of examination should be utilized in order to rule out every possibility of an organic basis for the irregularity. This is important, since often elimination of a somatic non-cardiac or cardiac cause of such an irregularity is the best form of therapy.

Cardiac arrhythmias of psychogenic origin, like those arising from organic causes, should be treated medically; for instance, during an acute episode of paroxysmal auricular tachycardia or flutter, the alarming symptoms of dizziness, unconsciousness or syncope must be handled as an emergency with the aid of drugs; one cannot expect psychotherapy to break such a paroxysm. Even though psychotherapy is being employed prophylactically in the treatment of some annoying arrhythmia, the therapist will find it most helpful in handling the patient if he could, at the same time, resort to simple drugs to reduce the incidence of its occurrence. The patient should be assured that the troublesome symptoms are caused by the cardiac irregularity, which experience has shown to occur in people without heart disease, and that the medicines are aimed toward the abolishment of arrhythmia per se and not toward the treatment of some basic organic disease. The drugs employed in the treatment of arrhythmias of psychogenic origin are similar to those used for cardiac irregularities arising from an organic basis.

Concluding Remarks

It has been the purpose of this communication to delve into a subject which, in many respects, is still on the frontiers of medicine. Much of the subject matter is still unknown or inadequately surveyed; little is clearly defined. An attempt has been made to blend together various developments from the fields of psychiatry, physiology, and classical cardiology, with the view of breaking down the provincial barriers of each field in its individualistic approach to the psychosomatic problem of cardiac arrhythmias. We are aware of the imperfections which the present effort contains, but are hopeful that it will be stimulating enough to encourage the explorer in the several disciplines to widen the scope and outline the topography of this unknown wilderness. There is danger that each will see and emphasize those peculiarities for which his background has trained him to search. However, it is not too much to expect that, ultimately and perhaps sooner than we imagine, each exploration will fit as a logical, integral part into this multifaceted problem, understandable and satisfactory to all.

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PRIMARY ATYPICAL PNEUMONIA *

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Primary atypical pneumonia is, in many respects, one of the most peculiar of the infectious diseases of man. In the past eight years many careful and extensive studies of the illness have been carried out. During World War II the disease occurred frequently and among military personnel the incidence was greater than that of all other forms of pneumonia combined. Since the war the incidence of the illness appears to have diminished markedly. Although there is now a considerable quantity of accurate information about the condition, there remain in an unsatisfactory state a number of important problems. From the clinical standpoint these are concerned chiefly with the establishment of the diagnosis, the differentiation of the disease from other forms of pneumonia, and its treatment. From the laboratory standpoint they are concerned chiefly with the etiology of the disease, with means whereby the diagnosis may be supported, and with the control of the condition.

In this paper present evidence regarding diagnosis on the basis of both clinical and laboratory findings will be presented and an attempt will be made to evaluate present information relative to etiology.

In primary atypical pneumonia the usual clinical picture [1] is the following: The onset is gradual and ill-defined; general complaints and constitutional symptoms are first noticed and commonly precede symptoms referable to the respiratory tract. Fever, cough, headache and malaise develop early and are among the commonest symptoms. Cough is almost invariably present; in its absence, the diagnosis is questionable. Usually the cough is non-productive and hacking at onset but later becomes productive; the sputum is mucoid or mucopurulent, seldom contains blood, and may be copious. Most patients do not appear very ill. Fever is usually not high and often remittent. The pulse rate is slow in relation to the fever; relative bradycardia occurs in two-thirds of cases and is of some diagnostic importance. The respiratory rate is usually normal at rest. Abnormal physical signs are not striking; often the presence of pneumonia is not suspected until roentgen-rays of the chest are taken. Roentgenograms usually show definite evidence of pneumonia; the pulmonary lesions vary widely in density and distribution. It is very doubtful that a diagnosis can be made from roentgenological evidence alone. Pneumonia is most frequently present in the lower lobes, but any area in the lungs may be affected. Consolidation may be present in more than one lobe and extension from one lobe to another may

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occur. The leukocyte count and differential patterns are usually normal. The erythrocyte sedimentation rate is increased. The blood culture is sterile. Cultures of the throat or sputum show the normal bacterial flora.

The course is extremely variable. On the average, fever is present for 10 days; the range is one day to seven weeks. The average maximum temperature is 103° F.; the range, 99 to 106° F. Fever usually falls by lysis and resolution often begins when the temperature comes to normal. However, evidences of consolidation may persist for some time. Complications are uncommon and rarely of much significance. Pleuritis occurs rarely. Hemolytic crises and anemia have been reported. Thrombophlebitis or bronchiectasis occasionally develop. The prognosis is in general excellent.

It is seldom an easy matter to establish a trustworthy diagnosis. To a large extent the diagnosis is one of exclusion. Often it is necessary to accumulate considerable clinical, roentgenological and laboratory data before the probability of error becomes small. A number of viral and rickettsial diseases may present very similar clinical pictures. These diseases are: psittacosis or ornithosis, Q fever or *Rickettsia burneti* pneumonia, influenza A, influenza B, and lymphocytic choriomeningitis. Pneumococcal as well as other bacterial pneumonias may be almost indistinguishable from primary atypical pneumonia. In children pneumonia associated with measles or whooping cough may present an analogous picture. Pulmonary tuberculosis, tularemia, coccidioidomycosis or toxoplasmosis may at times simulate the disease.

There are two laboratory procedures [2-5] which are helpful in supporting the diagnosis. Both are relatively simple tests which any good bacteriological laboratory should be able to carry out with ease. They are: (1) cold hemagglutination, and (2) streptococcus MG agglutination. Either test is best carried out with specimens of serum obtained at different periods during the disease, preferably at weekly intervals. If either serological test is positive, and especially if a significant increase in either type of agglutination titer is demonstrable some weeks after onset, there is a high probability that the diagnosis is correct. If both tests are negative, the diagnosis may still be primary atypical pneumonia, but to establish it beyond doubt under such circumstances is very difficult indeed.

The treatment of the disease is still in an unsatisfactory and nonspecific state. Supportive and symptomatic therapy similar to that used commonly in other forms of pneumonia is helpful but chemotherapy is of no avail. None of the sulfonamide drugs, even in very large doses, exerts a favorable influence on the course of the illness. Moreover, penicillin, even in massive dosage, is not beneficial. Convalescent human serum has been tried but has not produced any obvious effect. Fortunately, the mortality rate is very low, probably less than 0.5 per cent in previously healthy persons, and patients who appear to be severely ill generally recover from the infection. Second attacks have been observed occasionally and, therefore, it appears that the

disease is not always followed by the development of immunity against reinfection.

In 1943 it was shown that a number of very peculiar and unusual serological phenomena occur during the illness. Peterson et al.[2] and Turner[3] showed that the serum of patients may acquire the capacity to cause agglutination of human group O erythrocytes at icebox temperature but not at incubator temperature, i.e., cold-hemagglutination. Thomas et al.[6] found that during the disease the serum of patients may acquire the property of showing positive complement fixation reactions with a variety of animal lung tissue antigens, i.e., nonspecific complement fixation. As a result, transient positive Wassermann or Kahn reactions may be obtained during the illness. Thomas et al.[4] further demonstrated that in the course of the infection patients may develop in their blood specific agglutinins against a particular species of non-hemolytic streptococcus, i.e., streptococcus MG. These three serological reactions are caused by distinct and different components of serum.[5]

TABLE I

Serological Reactions in Primary Atypical Pneumonia
Summary of Published Data [2-6, 14-28]

Serological Test	Serum from Patients with	No. Patients Tested	Positive Test	
			No.	Per Cent
Cold hemagglutination	Prim. atyp. pneum.	801	454	56.7
Cold hemagglutination	Other diseases	1719	75	4.4
Cold hemagglutination	Normal persons	209	17	8.1
Strep. MG agglutination	Prim. atyp. pneum.	669	294	44.0
Strep. MG agglutination	Other diseases	568	23	4.0
Strep. MG agglutination	Normal persons	357	19	5.3
Complement fixation vs. lung antigens	Prim. atyp. pneum.	35	25	71.4
Complement fixation vs. lung antigens	Other diseases	23	0	0.0

Numerous studies on the serological reactions which are obtained in the disease have been carried out. A summary of published results [2-6, 14-28] is presented in table 1. It will be seen that positive cold-hemagglutination tests occurred in 56 per cent of patients with primary atypical pneumonia; at least 12 times more commonly than in other diseases. It will also be noted that positive streptococcus MG agglutination tests were obtained in 44 per cent of patients with primary atypical pneumonia; at least 10 times more frequently than in other illnesses. It is evident that with neither agglutination test are positive results obtained in all cases. Some patients show positive reactions with one test but not with the other. Consequently it is wise to carry out both tests as a routine. A significant increase, i.e., a fourfold increment, in titer in either test is only very rarely found in diseases

other than primary atypical pneumonia. In order to show such an increase in titer, it is necessary to test two specimens of serum, one taken early in the disease preferably less than one week after onset, and another obtained during the third or fourth week from onset. In obtaining serum from patients with the illness there is one simple precaution which should be observed. The blood is allowed to coagulate at room temperature and the serum is removed before the specimen is refrigerated. Once the serum has been separated from the clot, it may be stored at icebox temperature in the usual manner. If this procedure is disregarded and blood is allowed to coagulate in the refrigerator, the greater part or all of the component responsible for the cold-hemagglutination reaction will be removed from the serum and discarded with the clot. The results of cold-hemagglutination tests with serum separated after refrigeration will, in the great majority of instances, be negative.

It might be thought that cases which show positive cold-hemagglutination reactions or positive streptococcus MG agglutination reactions are examples of an illness different from that in cases which fail to show positive reactions in either test. This probably is not true. In both tests the serum titers commonly observed are not very high; in other words, neither test can be considered to be very sensitive. Moreover, in either test the incidence of positive reactions is directly proportional to the severity or the duration of the illness; the more severe the infection, the more probable is a positive serological reaction.[1, 23] It appears, therefore, that quantitative factors, e.g., the degree of illness or the extent of the infection, rather than qualitative factors, e.g., possible differences in cause, are decisive in determining the appearance of positive serological reactions.

In carrying out cold-hemagglutination tests most workers now use a 1.0 per cent suspension of group O erythrocytes. Serum titers of 1 : 40 or more are generally considered to be significant. A fourfold or greater increase in the titer of serum obtained during the third or fourth weeks, as compared to the titer of serum taken early in the disease, is of much greater significance and only very rarely occurs in any other condition.

In agglutination tests with streptococcus MG a 5 times concentrated and heat-killed bacterial suspension is satisfactory. Serum titers of 1:20 or more are considered to be significant. A fourfold or greater increase in agglutination titer with serum specimens similar to those mentioned above is almost never encountered except in primary atypical pneumonia.

There is now good evidence that the great majority of cases of the disease are not attributable to infectious agents, either microbial or viral, of definitely established pathogenicity for man.[1, 7] The following infectious agents are of little or no importance in the etiology: the psittacosis group and the influenza group of viruses; Q fever rickettsiae; and bacterial species commonly associated with pneumonia. However, a number of different infectious agents have been put forward as possible etiological factors.[8-13] Many attempts have been made to recover the infectious agent or agents

responsible for the disease, but there is not yet complete agreement among investigators as to the nature and identity of the causal agent. Two kinds of studies have been carried out; in one, attempts were made to transmit the infection to laboratory animals; in the other, attempts were made to transmit the infection to human volunteers.

The various results obtained in laboratory animals are confusing and conflicting. A summary of published data[8-13] is presented in table 2. It appears that at least five different infectious agents, each of which may be a virus, have been implicated as possible etiological factors. It is, of course, possible that a variety of different infectious agents are capable of inducing

TABLE II

Studies on the Etiology of Primary Atypical Pneumonia
Summary of Published Data

Reference	Susceptible Experimental Animals	Filterable Agent	Evidence for Neutralizing Antibodies in Patients
Stokes et al.,[8] 1939	Mice, guinea pigs, ferrets	+	0
Weir and Horsfall,[9] 1940	Mongoose, chick embryo	+	+
Blake et al.,[10] 1942	Cats, kittens	+	+
Eaton et al.,[11] 1942	Cotton rats	+	0
Horsfall et al.,[12] 1943	Cotton rats	+	+
Eaton et al.,[13] 1944	Chick embryo, hamsters, cotton rats	+	+

the disease, and that at different times and places one or another of these agents was recovered. However, it should be pointed out that none of the reports concerned with filterable infectious agents has been confirmed by an independent report from another laboratory. Unfortunately, all of the agents which have been claimed to be transmissible to laboratory animals possessed properties which made experiments difficult to carry out and the results obtained even more difficult to interpret. The results of virus neutralization tests with sera from patients were considered to indicate that neutralizing antibodies against most of the agents had developed during the illness. Convincing evidence for the development of antibodies against a virus would provide strong evidence in favor of a causal relationship. However, because of the very peculiar serological phenomena which are associated with the illness and the very low pathogenicity of the infectious agents so far employed, it is doubtful that unequivocal evidence for the development of antibodies against a virus has been obtained.

The results of experimental transmission of the disease in human volunteers carried out by the Commission on Acute Respiratory Diseases [29] appear to have been more decisive than results obtained in laboratory animals. Among 60 men who were inoculated with pooled specimens of throat washings and sputa obtained from patients, 16 developed an illness which was thought to be primary atypical pneumonia, whereas 26 others developed so-called minor respiratory illness without pneumonia. It was shown that

bacteria-free filtrates were capable of inducing the disease in man and that the experimental infection could be transmitted a second time in volunteers. Among the 16 volunteers in whom the disease was apparently induced, 13 developed cold hemagglutinins and two also developed agglutinins against streptococcus MG. These workers concluded that the results of their studies indicate that the disease is at least initiated, if not caused, by a filter-passing agent, presumably a virus.

Not only have various viruses been suggested as etiologic agents in the disease, but also a bacterium has been implicated in the pathogenesis. A single serological type of non-hemolytic streptococcus, now designated streptococcus MG, was isolated from the lungs of fatal cases.[5] As has been indicated, agglutinins against this microörganism develop in the serum of approximately 44 per cent of patients. Present evidence indicates that the various serological reactions obtained with streptococcus MG are caused by specific antibodies against it which are separate and distinct from the serum components responsible for cold-hemagglutination and nonspecific complement fixation. There appear to be three possible explanations of the serological findings with respect to streptococcus MG. First, they may be due to a coincidental immunological relationship to the actual causal agent. Second, they may be due to secondary invasion by streptococcus MG. Third, they may be the result of a so-called complex or double infection initiated by both the streptococcus and some other infectious agent, presumably a virus. There are some reasons for thinking that the first two explanations are improbable. However, it has not been possible, as yet, to obtain direct and conclusive evidence in favor of the theory of complex infection.

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THE GENESIS OF THE NEUROSES *

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THE Second World War focused much attention upon the psychoneuroses, and to many the fact that over a million of our young men were not fit for military service because of psychoneuroses was a jolt. Much has been written about the rôle of the war in the production of the psychoneuroses—but military service did little more than act as the precipitating factor, since almost as many young men were rejected for service as were dismissed from the armed forces because of neurotic disorders. Psychoneurotic illness has always been with us, and I do not believe it will ever be eliminated as a major cause of discomfort and disability.

Before proceeding to any discussion of a disease it is well to define it, though the difficulties of presenting an entirely satisfactory definition will be appreciated. To me a psychoneurosis is a group of symptoms which may be physical, mental, or both, which develop in an individual when he is incapable of dealing successfully with the circumstances in his life at a given time. His powers of adaptability are inadequate in the face of the complexities of the present situation. There are two implications in this definition of which I hope you will make note: first, that neuroses occur in response to demands made upon the individual. These demands may come from without or from within the person. Secondly, observe that this definition implies that recovery from a neurosis is possible. Improvement may be brought about either by reduction of the demands upon the individual or by the acquisition of additional knowledge and understanding, by which his ability to adjust or cope with the situation is improved. The former method is exemplified by the regimen which requires a long rest "getting away from it all," or some other procedure which masks the situation or otherwise diminishes the pressure. The latter method is best illustrated by a program of psychotherapy which increases the person's adaptive powers.

Before discussing the genesis of neuroses I would like to recall an old facetious comment that "Life is a funny proposition; man is born into this world without his consent, leaves it against his will, and finds the voyage between exceedingly rough." The fact that life has been more onerous for some persons than others explains why some develop personality and adjustment difficulties while others are much better adjusted. In considering what the real difficulties of life are we are inclined, because of our training as physicians and the dominance which pathology has held over us, to think in

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terms of material things; consequently an individual's environment is frequently evaluated by whether or not he has known poverty or whether his family has been successful, respectable and intelligent. When the answer to these questions is favorable we often hear expressions of mystification that the son or daughter of such a family can be such a misfit. Let this attitude be improved by appreciating that "man does not live by bread alone."

Recent advances in psychiatry have led to an appreciation of the fact that we have been prone to ignore the experiences of early years, and the rôle they may play in the production of psychoneuroses. Freud and his followers have successfully and wisely focused attention on the early experiences in life. We recognize that the span of life within our memory has been one in which there has been considerable conflict, but forget that the period beyond our recall may be even more difficult. Immediately upon our arrival in this world we begin to experience new sensations, and soon have restraints placed upon us as we endeavor to gratify the instinctive drives which assert themselves. By the time we become aware of the nature of social restraints we try to adapt our actions and thinking so we will attain gratification in a form and under circumstances approved by society, of which we aim to become an acceptable member. We are constantly striving toward a better integration with the society in which we live, to try to find purpose in our existence, with gratification of our inward drives in such a way that we acquire satisfactory self-esteem. In our drive toward maturity we strive to arrive at a hetero-sexual adjustment, find an appropriate love object of the opposite sex, live in harmony with the members of our family and society, and abide by their customs and dictates. The individual who attains these objectives we may regard as one who is mature.

Briefly let us consider life from its beginning. After conception a time arrives when the embryo develops to the point where it is capable of consciousness of its own existence. The in utero existence of the individual is rather an idyllic one in which all the bodily needs are taken care of by the host, the mother. It lives in a water cushion, protected from injury in a most satisfactory way. As the time of gestation approaches its termination the unborn undergoes some new and unpleasant experiences as the preliminary contractions of the uterus arouse consciousness to the point of appreciating uncomfortable sensations. As these contractions become the labor contractions its previous state of tranquillity is disturbed as it is squeezed and forced into the birth canal. Reflexly it participates in its own birth by attempts at extension of its body, forcing itself downward through the canal, and eventually as it arrives in this world, nearly in a state of exhaustion, it is suddenly projected into our midst. After some harsh manipulation including a few spanks on the back, the infant breaks into his first cry which I believe is one of protest rather than elation. Soon after voicing his resentment he falls asleep, a state of diminished consciousness which resembles that in which he previously existed in utero. He awakens to be assailed by

new sensations, among them being hunger as well as irritation at the swaddling clothes which are not as comforting to his skin as was the amniotic liquid. He is nursed; he falls asleep, and as this process repeats itself he soon begins to appreciate the pleasant experience of suckling, of having nice warm food enter his stomach and agreeably end the uncomfortable sensation of hunger. At the time he is held to the breast he experiences the external warmth of the mother's body and her fondling, and wishes its repetition. He rejects the unpleasant sensations of hunger, cold, noise and many others that occur to him in early life. Among the things he may find unpleasant and reject is noise, including the booming voice of the father as well as his rough manipulations. When pleasant and comforting experiences are provided in abundance we will have the happy, contented, well behaved infant off to a good start, but he may still experience mismanagement in later infancy with resulting frustration and deviation into a neurotic pattern.

As the infant lives out the early months of life and becomes aware of his existence he soon appreciates that he has and knows comfort through the bounty of persons outside himself. He is utterly dependent, and when those upon whom he depends fail to meet or anticipate his needs, he may experience anxiety or fear. When the gratification of his needs is suddenly interrupted he may often be noted to respond with obvious anger. A few months ago I was visiting at the home of young friends as the mother was nursing her two month old son. A caller necessitated the brief interruption of the nursing of the baby. As the infant was laid upon a couch he gave a beautiful demonstration of absolute rage, and when the mother returned to the nursing she was forced to wince in response to his angry bites of protest. So, to any observer, emotion may be detected in the early weeks of life. The absolute state of dependency is gradually eliminated as the child acquires new powers, e.g., the ability to move and thereby get away from unpleasant situations, or through movement to create pleasant sensations. Hence we have observed many youngsters roll their heads and flap their extremities in great glee as they experience the new power of control over their muscles and the exhilarating sensations of self-desired movements.

In a short presentation it is impossible to continue the visualization of this hypothetical child through the various stages of his development, but soon, because of his newly acquired power to move about, it is necessary to exercise restraint and supply guidance. This usually falls to the lot of the mother to whom the child is strongly attached; if she is kindly, patient, and intelligent, and endeavors to transmit to the child her reasons for the restraint the child suffers a minimal amount of anxiety, but when he is subjected to harsh and inconsiderate methods his anxieties may become almost overwhelming. Society, through the mother or mother-surrogate, is constantly endeavoring to mold the child into a pattern of acceptable behavior, and one of the demands of society is that of bodily cleanliness. Consequently

toilet-training is essential but it should never be begun until the child is entirely capable of appreciating the need of cleanliness. There has been no greater absurdity than the tendency of the pediatrician to begin toilet training at the age of one or two months. If the child is led and directed rather than coerced, and receives in exchange for his own efforts some reward and increase in his self-esteem he gradually acquires toilet-training as he does other acceptable traits. However, when he is coerced he may, because of his resentment, retard toilet-training accomplishments to a late date as one of the most satisfactory ways of expressing his resentment and hostility toward the mother or mother-surrogate. An effort should be made not to force upon a child a pattern of behavior for which he is not ready. Do not demand more adult performance than that of which he is capable.

Before we progress further I would like to speak of the importance of the atmosphere in the home that is created by the parents. If it is one of peace and tranquillity it is one in which the handling of the child will assuredly be considerate. But if the home atmosphere is filled with bickering and a great deal of tension, the child soon begins to respond with manifestations of fear. I would like to speak very briefly of a child under my observation almost from the time of birth although only as a "friend of the family." The mother was well known to me as a youngster prone to outbursts of terror at the sight of a horse, dog or some strange object. She was also given to outbursts of temper and breath-holding, which demonstrations of fear and anxiety "according to the neighbors" made her own mother a nervous wreck. I was present on one occasion when after becoming a mother she was nursing her firstborn child, then about two months old. The quiet was suddenly shattered by the backfiring of a truck, whereupon the mother jumped; the breast fell out of the child's mouth, and immediately he showed absolute terror as he was almost dropped from the mother's arms. I do not consider this incident a determining factor in the child's life. However, I had the opportunity of observing the same child shortly after he was two years old when as strangers entered the room he jumped from the mother's lap and hid behind a chair. Then a dog belonging to the newcomers came into the room suddenly, whereupon the child scrambled into his mother's lap with a scream. As the dog rushed forward to investigate the noise, the mother joined the child in the screaming, and in far less time than it has taken me to tell you of it the child began to vomit down the mother's back; the mother fainted and required restoratives. The two year old child was distinctly a neurotic; call the mother what you wish. I have been informed by those who have known the child all through his life that he has vomited whenever the slightest event occurred creating noise, tension or anxiety in the household.

I am sure many of you are already disappointed and possibly are feeling anxiety because I have not mentioned that which some of you have been led to believe is the principal cause of all neurotic disturbances, namely, sex.

I am certain that this attitude—of sex being so largely responsible for neurotic behavior—is one that has become established as a result of the fly-by-night adherents of Freud who have disseminated inadequate understanding of his principles. At any rate it has been the experience of psychiatrists to discover that most physicians regard sex as of tremendous importance in the genesis of the neuroses. Not only is it considered the principal cause but many are prone to regard sex relations as a most beneficial therapeutic procedure. It is not unusual to see patients who have been advised to marry in order to recover from their neuroses, or worse yet, advised to seek sex experiences as a therapeutic measure. Sex, as a therapeutic measure, is the only thing I know which may be more over-rated than Southern cooking.

The sex instinct is basically a drive for love. As I have already indicated, the child's first love is the love of his mother because she means so much to his well-being. He naturally is anxious to retain that love for himself, and when he sees the father in a rival rôle for the time and affection of the mother it may be the source of infantile anxiety. It is not at all unusual to hear a child express the intention of shooting his father and marrying his mother when he is grown up. You may have observed it in your own experience. As the child broadens his field of activities he strives for the affection of others and for manifestations of their approval. By such experiences and the incident rivalries the child acquires knowledge and improves his adaptative powers. As this occurs he becomes less dependent upon the mother, and some of his desires for affection and love are gratified by his experiences with other children. Little boys and girls at the age of six or seven are devotedly attached to each other and derive from each other a great deal of gratification. It is inevitable during this time and even earlier that boys will discover their sex organ; it is during this period that sex play between children is going to develop since it is motivated by curiosity, and during this time of life one of the major trauma occurs. First of all the mother may wish to retain the affection of the child permanently; she scolds him because he has reached a point where he likes to spend more time with the children next door than with her, etc. It is also a time when mothers discover the tendency of their children toward sex play and their desire to acquire understanding of sex, and mothers often rebuke children or fail to give them proper answers and so behave that they build up strong feelings of guilt around matters of sex. Then there comes a time when society separates children according to sex; this is definitely a period of homosexual attachment. It is axiomatic that if one has not learned simple arithmetic, such as the multiplication tables, one cannot progress to a satisfactory understanding of long division or algebra. So the child who has not had the opportunity of passing through these various phases of emotional development cannot become competent in the more intricate pattern of adult living. As a consequence a heterosexual adjustment may be difficult or impossible

to achieve. It is our failure to appreciate that the sex urge is basically a drive for the affection of desirable individuals; that it is essentially innocent and without guilt until our culture makes it so, that impairs the ability to adjust satisfactorily. Much has been written about the giving of sex information to children, and we can only generalize by saying that when a child asks questions about sex the parent should give a simple, honest answer to satisfy the child's need at that moment. Parents must not act as though it was something which made them very uncomfortable, for by such attitudes they may raise anxiety in the child's mind. Then in the future the youngster will avoid asking any questions, and the parents will have lost the golden opportunity of participating in their child's development.

I would like to speak of one other strong instinct and comment on the handling of it in society. We all know the child has a strong self-acquisitive instinct, and in early life we are all guilty of many acts of petty thievery. This instinct, like that of sex, never leaves us; as we grow older we still have the "Gimmies" and "I wants," but very few of us, if any, are thieves because our mothers, who understand that children are going to steal a little bit, are patient, and eventually they carefully point out to children the property rights of other individuals. Ultimately, the child learns that there are proper and improper ways of acquiring property, and to follow the accepted way becomes essential because the approving attitude of others does help to develop our self-esteem. If a similarly intelligent, patient, and consistently applied attitude could be adopted toward sex, anxieties about sex would be no more disturbing than the fact that when we do not make as much money or have as much of the world's goods as we would like to have we do not feel guilty but exert efforts to gratify our acquisitive instinct through increased effort.

In this short presentation I have tried to focus attention upon the importance of the very earliest weeks and months of life in the eventual formation of personality. I have tried especially to indicate that the love life of the child begins with his attachment to the mother, that it progresses through attachment to other individuals, especially to children, and passes through a period of strong homosexual attachment before it arrives at a final heterosexual adjustment. At this point I would like to indicate that a heterosexual adjustment does not imply that to be adjusted adequately at the heterosexual level an individual must have sex relations.

If during any of the periods of growth the child does not experience normal gratification and is not afforded satisfactory opportunity for development and adjustment, a neurotic pattern may be established. The pattern may continue throughout life or may be improved as a result of favorable influences. In the latter instances some deficiency may remain and in later life, under difficult circumstances, the pattern of neurotic behavior may again assert itself.

Before closing I would like to speak briefly of measures which I feel can contribute to the prevention of many psychoneurotic and maladjusted per-

sons. The etiology of the neuroses is now rather well understood, though there are many gaps to be filled in the knowledge which we possess. With the knowledge we do have, the psychiatrist is capable of effecting a cure in a large percentage of patients, and from this experience we are gradually evolving methods for the prevention of neuroses. As with every true physician, efforts toward prevention must be intensified by the psychiatrist to serve the public best. As knowledge of the prevention of physical illness has increased, mothers have shown an intense interest and have endeavored to avail themselves of all prophylactic measures. Their knowledge of the dietetics of infancy has diminished infant dysentery and other gastrointestinal disturbances. These same mothers are just as anxious to have made available to them knowledge which will enable them to rear more satisfactorily adjusted children. Because of this I feel the psychiatrist must make available to these mothers that knowledge which will be helpful, through integrating their services with the prenatal and well-baby clinics. The general practitioner and pediatrician must become better informed and more capable of acting as advisers to mothers on matters pertinent to the emotional development of infants and children.

CASE REPORTS

THE ETIOLOGY OF BANTI'S SYNDROME; FURTHER SUPPORT OF THE "CONGESTIVE SPLENOMEGALY" HYPOTHESIS *

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Banti, in describing the syndrome which bears his name, attributed the condition to an unknown toxin acting primarily on the spleen. This concept was questioned as early as 1904 by Dock and Warthin,[1] who described two cases of Banti's syndrome associated with stenosis and calcification of the portal vein. These investigators believed that the histological changes in the spleens of these cases could be explained by prolonged passive congestion and suggested the possibility that the clinical picture might be caused by portal vein stenosis. Subsequently Dürr [2] observed that sections of the spleens from Banti's original cases showed pathological changes indistinguishable from those found in the spleen in cases of cirrhosis of the liver. Warthin [3] reviewed many cases of Banti's syndrome and concluded that in at least some cases the condition was a result of portal or splenic vein obstruction. Larrabee [4] studied the records of 47 cases of the disease and was "forced to the conclusion that most if not all of these cases were not only associated with lesions interfering with the outflow of blood from the spleen, but were actually the results of such lesions."

The "congestive" theory of the pathogenesis of Banti's syndrome has been given very strong support by the recent clinical and experimental studies in the Spleen Clinic of the Presbyterian Hospital in New York.[5, 6, 7, 8] It appears that the syndrome characterized by splenomegaly, anemia, leukopenia and increased collateral circulation between the portal and systemic venous beds is the usual result of splenic vein hypertension. Cirrhosis of the liver, formerly looked upon as a regular feature of Banti's syndrome, is now recognized as etiological in some cases because of the portal hypertension which it produces. However, in cases in which portal obstruction is extra-hepatic, cirrhosis does not occur.[8] Many cases of Banti's disease have now been described in which a variety of obstructive factors have been demonstrated, including cirrhosis of the liver, thrombosis of the splenic or portal vein, cavernomatous transformation of the portal vein and portal stenosis. The clinical and pathological studies which have already been made would seem to leave little doubt as to the veracity of the "congestive" etiology of Banti's syndrome. Nevertheless, there are still some, e.g. Ravenna,[9] who are unwilling to accept this evidence and it is for this reason that the present case is reported.

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From the AAF Regional Hospital, Maxwell Field, Alabama.

Case Report

A 33 year old white housewife was admitted to the hospital on December 11, 1944 because of hematemesis starting six hours prior to admission. The family history was non-contributory. The patient was born and had always lived in Alabama. She had been married for four years but had no children. Before the onset of her present illness she had had no important sickness. She smoked an occasional cigarette but never used alcohol. She denied having taken drugs or having been exposed to any toxic agents.

She stated that she had been in excellent health until 1936 when at the age of 25 she suddenly and without antecedent symptoms had a large hematemesis. She was admitted to a hospital where she was told that she had an ulcer of the stomach. She was placed on a strict ulcer regimen but the gastric hemorrhage persisted and was controlled with great difficulty. After the cessation of bleeding she became asymptomatic. However, following this occurrence she had similar severe hematemeses once or twice a year. In the interval between bleeding episodes she felt quite well with no gastrointestinal or other symptoms. She had never had jaundice or ascites.

About one year before admission she had two episodes of very severe hematemesis within three months. Therefore, in January 1944 she was admitted to another hospital where she was studied and a splenectomy was performed. She was told that her liver appeared normal. She had an uncomplicated recovery from the operation and remained in good health until the day of admission to this hospital. About six hours before admission she began to feel faint and dizzy. She then became nauseated and vomited about a half-pint of bright red blood. Several hours later she vomited about an equal quantity of dark blood. She was then brought to the hospital.

On admission she was ambulatory and in no acute distress. She was pale but well developed and well nourished and did not appear to be very ill. Temperature was 98° F., pulse 88, respirations 20 and blood pressure 102 mm. of mercury systolic and 55 diastolic. Aside from pallor the skin and mucous membranes were clear with no spider angiomata, edema, or jaundice. There were no dilated veins visible on the thorax or abdomen. Examination of the head and neck was not remarkable. The heart and lungs were normal. There was a healed midline upper abdominal scar. The abdomen was soft and not tender. There was no evidence of free fluid. The liver was not palpable nor were any other organs or masses felt. The remainder of the physical examination was negative. Red blood count on admission was 4,200,000, hemoglobin 12.3 grams (84 per cent), white count 19,200 and platelet count 260,000.

She was given morphine but shortly after admission again vomited a large quantity of blood. Thereafter hematemeses were frequent and severe. She was repeatedly transfused but it was not possible to replace the blood as rapidly as she lost it. In less than 24 hours after admission she died of hemorrhagic shock.

Blood was drawn for chemical tests about eight hours after admission. The persistent hemorrhage and repeated transfusions make the results of some of these tests of little significance. Non-protein nitrogen was 29 mg. per cent, cholesterol 214, bilirubin 1.1, phosphorus 2.4, phosphatase 2.6 Bodansky units, total protein 5.3 per cent, albumin 2.8 per cent and globulin 2.5 per cent. Cephalin flocculation was two plus and sedimentation rate 24 mm. in one hour.

It was felt that this patient did not have cirrhosis. There was no history of alcoholism and there was nothing in the history or physical findings which suggested liver disease. Furthermore, she had been told following splenectomy that her liver appeared normal. Therefore, we believed that her Banti's syndrome was caused by an extrahepatic obstruction of the portal circulation. The clinical examination gave no clue as to the nature of this obstruction. The clinical diagnosis was Banti's syndrome secondary to extrahepatic portal obstruction of unknown nature with death resulting from rupture of esophageal varices.

At autopsy the significant findings were limited to the abdomen. The peritoneal cavity contained no free fluid. The liver weighed 1160 grams and appeared to be normal. The spleen had been removed, but in the splenic bed, coursing over the pancreas, were numerous tortuous, greatly dilated veins establishing collateral circulation between the splenic vein and the veins of the stomach. The branches of the portal system were enlarged and the portal vein itself was dilated. A careful dissection of the portal vein revealed that just as it entered the liver the vein was thrown into a sharp "S" turn and its lumen was reduced to about 2 mm. Beyond this constriction the vein terminated abruptly in a small saccular dilatation from which several minute branches extended into the right lobe of the liver. These branches were so small that they would hardly admit the end of a probe. No branch to the left lobe of the liver could be demonstrated. There was no evidence of scarring or thickening of the almost blind end of the portal vein and the intimal surface appeared to be normal. It was apparent that very little portal blood could have entered the liver through this anomalous vein. Microscopic examination revealed no abnormality of the liver except in one small area where there was a focal collection of small round cells. There was no evidence of cirrhosis. The stomach was distended, containing about 1500 c.c. of fresh blood. In the posterior wall of the cardia 1.5 cm. below the esophageal junction were three elevated ridges running in the long axis of the stomach and having the gross appearance of rugae. At the esophageal end of the largest of these was a punched-out purplish erosion 2 mm. in diameter. On section the longitudinal folds were seen to be produced by large varices within the wall of the stomach. The eroded area in the gastric mucosa opened into one of these vessels and was the source of the fatal hemorrhage. The abdominal viscera were otherwise normal except for dilatation of the venous channels in the submucosa of the gastrointestinal tract.

Subsequently a report was obtained from the hospital in which the patient had had her splenectomy. The records showed that on admission to that hospital in January 1944 physical examination had revealed an enlarged spleen. The liver was not palpable and there were no other significant physical findings. Laboratory studies done at that time included a red cell count of 3,520,000, hemoglobin 59 per cent, white cell count 2400 with normal differential count, and platelet count 144,000. Bleeding and clotting time and a red cell fragility test were normal. Sternal marrow biopsy showed no abnormalities except that the marrow was perhaps slightly hyperplastic. She was considered to have Banti's disease and a splenectomy was performed. The spleen was adherent to the omentum, diaphragm and adjacent peritoneal surfaces. There were tremendous veins as large as a finger running into the spleen from every side. The liver appeared to be normal. The spleen weighed 550 grams. The capsule was thickened and on section the organ showed a notable increase in fibrous tissue. The Malpighian bodies appeared compressed and reduced in number. Perivascular fibrosis was most prominent around the veins. The findings were considered to be consistent with a long standing passive congestion corresponding to the morphological picture seen in Banti's disease.

Discussion

This case is reported in further support of the "congestive" hypothesis of the pathogenesis of Banti's syndrome. A number of very similar cases have previously been described,[8] in which the cause of the splenic vein hypertension was an extra-hepatic obstruction of the portal or splenic vein. Ravenna[9] believes that the finding of such lesions as thrombosis, stenosis or cavernomatous transformation of the portal vein does not prove the congestive etiology of Banti's disease and thinks that these lesions are secondary to a primary disease

of the spleen. A significant feature of the present case is that the obstructive lesion was unquestionably a congenital anomaly and therefore the primary cause of the portal hypertension. We believe that the age to which our patient lived before her first hematemesis is quite remarkable in view of the nature of her lesion.

Congenital anomalies of the portal vein producing portal hypertension are apparently rare although they have been previously described.[10, 11] Thompson[7] reported a small group of cases in which the obstructive factor was thought to be an anatomical defect or thrombosis of the portal vein occurring at or before birth, but the exact nature of the lesion was not proved in his cases. Perhaps a more careful search for such anomalies at autopsy in young individuals dying with the Banti type of picture might reveal a higher incidence of such lesions.

In this regard, an important feature of the present case is the difficulty with which the obstructive lesion was demonstrated. It would have been absolutely impossible to have found the obstruction at operation, even with the most careful exploration. At autopsy the lesion almost certainly would have been overlooked had it not been painstakingly sought. The portal vein appeared dilated but otherwise normal as it entered the liver and its almost blind-end termination was discovered only when its course was traced into the liver substance. Warthin[3] commented on the relatively large number of cases of splenic anemia reported without mention of portal or splenic vein obstruction and pointed out that these veins are not thoroughly examined at the usual autopsy. In this connection the case of Trimble and Hill[12] is of interest. These authors described a patient with Banti's syndrome in whom a stenosis of the portal vein was overlooked at autopsy. This important lesion was found only on reëxamination of the specimen after attention was called to the significance of such an examination.

As in previously reported cases of extra-hepatic portal obstruction, the liver in our patient was normal in spite of the very long duration of the portal obstruction. This finding again confirms the belief expressed by Thompson[7] that cirrhosis occurs in Banti's disease only when it is present as the obstructive mechanism.

In view of our present knowledge a diagnosis of "Banti's disease" is no longer adequate. In every such case the underlying pathogenetic lesion should be sought. This is particularly important since the advent of new therapeutic technics. To some extent the prognosis and treatment of the condition depends upon the nature of the causative lesion. Splenectomy in all cases tends to cause the blood picture to return to normal. The anemia, leukopenia and thrombocytopenia appear to be a direct result of the presence of the congested spleen and usually disappear following its removal. Furthermore, splenectomy may reduce the volume of the portal circulation and thus relieve some of the burden placed upon the collateral circulation. When the obstructive lesion is limited to the splenic vein splenectomy may be curative. New procedures in vascular surgery by which portal-caval shunts may be produced may offer hope of prolonged life to patients with portal hypertension.[13] When the obstructive lesion is a disease process such as cirrhosis, the underlying disease should be treated. As with other disease processes, intelligent treatment requires an understanding of the disordered function.

Conclusions

1. A case of Banti's syndrome is described in which the causative lesion was a congenital obstruction of the portal vein at its termination within the substance of the liver.

2. This case is offered as further evidence in support of the "congestive" origin of Banti's syndrome and is thought to be of special significance because of the congenital and therefore obviously primary nature of the obstructive lesion.

3. The difficulty in demonstrating the obstructive lesion in this case again emphasizes the importance of very careful exploration of the portal and splenic veins at autopsy in all cases of Banti's syndrome.

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PRIMARY SPLENIC HODGKIN'S DISEASE WITHOUT LYMPH NODE INVOLVEMENT *

By Norman H. Isaacson, M.D., Samuel D. Spatt, M.D., and David M. Grayzel, M.D., Ph.D., *Brooklyn, New York*

In 1832 Hodgkin [1] called attention to the existence of a disease characterized by progressive enlargement of the lymph nodes and associated in many instances with enlargement of the spleen. Seventy-five years later Reed [2] stated "we know of no case where the pathological anatomy was described in sufficient detail to permit of a positive diagnosis in which the disease commenced elsewhere than in the lymph nodes." Even today most medical authors deny the existence of a primary splenic form of the disease.

Symmers,[3] however, in 1909 described a case of an 18 year old girl with recurrent chills and fever and a progressively enlarging spleen. The pathological picture in the spleen removed at operation was typical of Hodgkin's disease. No superficial lymph nodes were palpable and no enlarged nodes were found in the abdomen at operation. The patient died soon after operation, but unfortunately necropsy was not done. Hence examination of the mediastinal nodes, a frequent site of involvement, was not possible. The same criticism can be made for Wade's [4] and Dowd's [5] cases in which splenectomy alone was performed.

The first authentic report of a primary splenic form of the disease was by Krumbhaar [6] in 1931 in which there was extensive involvement of the spleen and bone marrow at autopsy, but no evidence of Hodgkin's disease in any of the lymph nodes. Similar cases were reported by Sears and Black [7] in which the thymus was also involved, and by Bordoni-Possi, Rurriel, and Ardao [8] in which the spleen alone showed the typical Hodgkin's picture. No bone marrow studies were done in the latter case. Finally, Gebauer [9] described a case with isolated involvement of spleen and bone marrow in which an antemortem diagnosis was made.

Case Report

B. P., a 62 year old white male, was first admitted to The Jewish Hospital of Brooklyn on September 28, 1945 complaining of swelling of the ankles of six to eight weeks' duration and exertional dyspnea for the same period of time. For the past 10 years he had been unable to work because of severe weakness. He was occasionally told he was "yellow" in the last six months and had lost 25 pounds in weight during the last year. He had been accustomed to drinking four to five glasses of whiskey a day until 10 years before admission but drank only occasionally since then.

The positive findings on admission were a nodular liver palpable three fingers'-breadth below the right costal margin and a spleen palpable four fingers'-breadth below the left costal margin. There was also brawny non-pitting edema of both ankles. His blood count at this time showed a hemoglobin of 34 per cent, a red blood count of 1.98 million per cu. mm., a white blood count of 2209 with 40 per cent polymorphonuclears, 2 per cent bands, 55 per cent lymphocytes, and 3 per cent monocytes. The smear showed anisocytosis, and basophilic stippling with 30 normoblasts. Bone marrow studies showed many "smudge" forms. There was no

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From the Department of Laboratories, Jewish Hospital of Brooklyn.

evidence of erythroblastosis. Roentgen-ray examination of the esophagus showed no evidence of varicosities. Studies of the lower femora (Gaucher's disease was suspected) showed only bilateral phlebosclerosis. Except for a cephalin flocculation of 4+ the liver function tests and all blood chemistries were within normal limits. The red cell fragility was normal.

A diagnosis of Laennec's cirrhosis was made and the patient was treated with vitamins, crude liver extract and blood transfusions and discharged October 31, 1945 when his hemoglobin had been raised to 51 per cent and he felt improved.

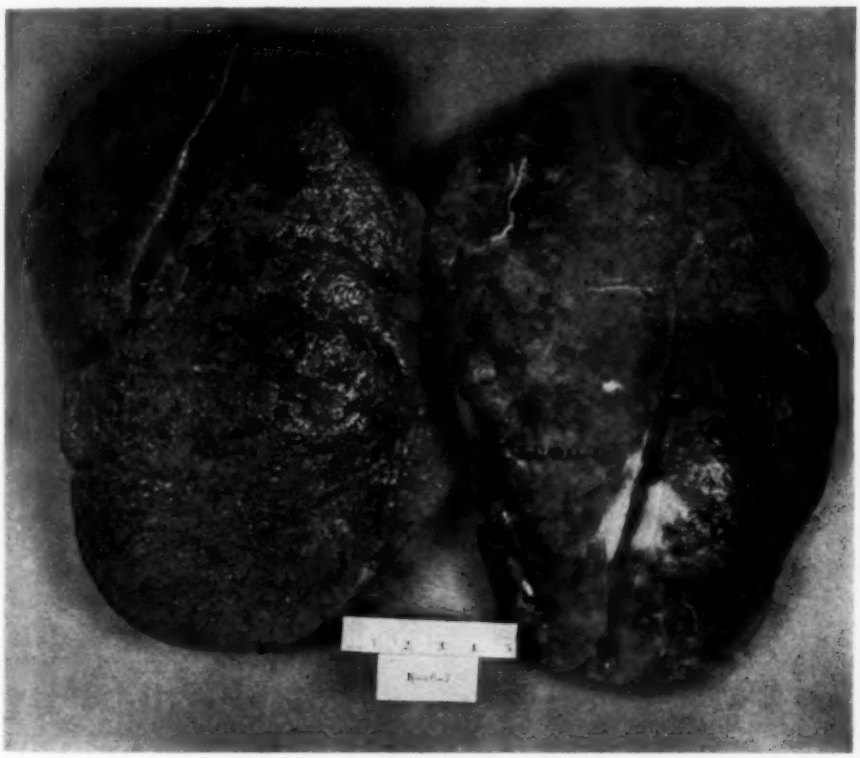

FIG. 1. Photograph of spleen showing fibrosis and an infarct in the lower pole.

He was readmitted on December 4, 1945 complaining of weakness, loss of appetite, shortness of breath and sharp pain in the left upper quadrant on coughing or deep breathing. He had lost 5 lbs. in the 10 days before admission. The liver was now palpable 5 cm. below the right costal margin and was not nodular. The spleen was estimated to be three times normal size. The blood and bone marrow pictures and blood chemistries remained unchanged. He was again treated with vitamins and crude liver extract and discharged December 30, 1945 subjectively improved.

His final admission was on January 7, 1946 when he entered complaining of chills and fever and pain in the right chest for four days. His lips were cyanotic and his skin yellow-tinged. He had wheezing respirations throughout the chest, moist râles at both bases, diminished breath sounds and dullness at the right base. There was a blowing systolic murmur at the apex of the heart. The liver and spleen were both palpable four fingers'-breadth below the costal margins. The liver was not nodular.

The blood count showed a hemoglobin of 32 per cent, red blood count 1.56 million, white blood count 4100 with 2 per cent polymorphonuclears, 8 per cent bands, 86 per cent lymphocytes, and 4 per cent monocytes. Despite vitamins, massive doses of penicillin and digitalis the patient went rapidly downward and died on January 11, 1946.

Autopsy: At postmortem examination done four hours after death, the body was that of a well developed and well nourished white male measuring 157 cm. in length.

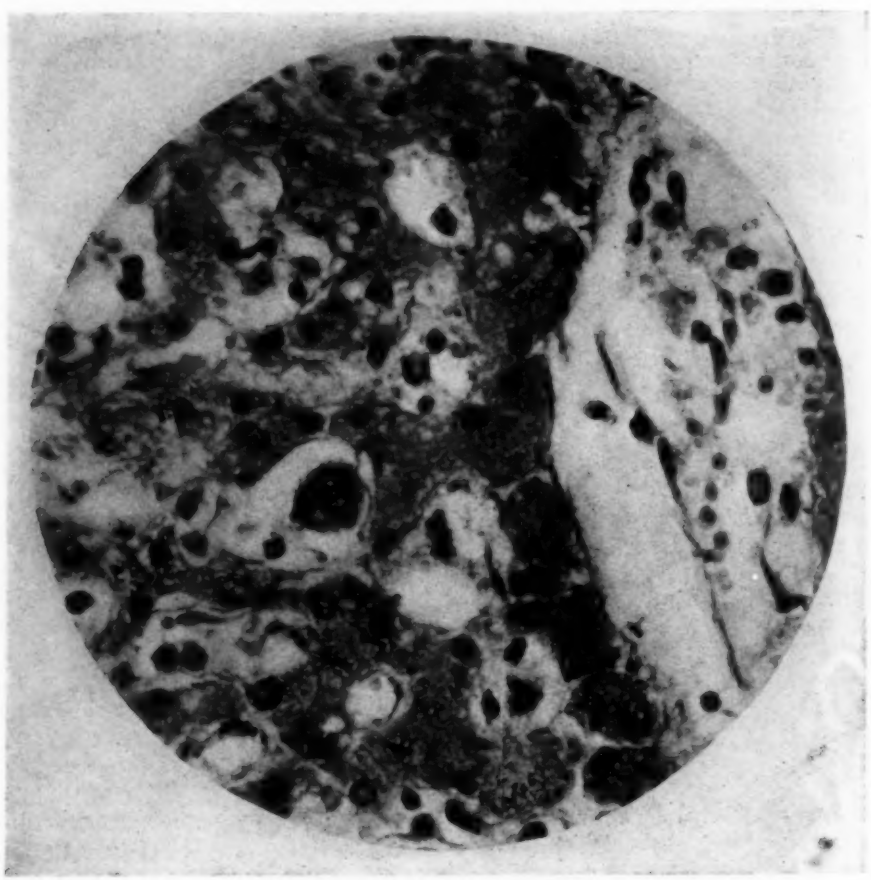

FIG. 2. Photomicrograph of liver showing pigmentation of liver cells and large cells in sinusoids. H & E × 320.

No external lymphadenopathy was present. The skin and sclerae showed a faint yellow tinge and there was a 2+ brawny non-pitting edema of both ankles. There were 200 c.c. of clear yellow fluid in the peritoneal cavity and firm adhesions at the apices of both lungs.

Heart and Aorta: The heart was of normal size and showed some white streaking in the left ventricle near the septum.

Respiratory System: The entire right lung was firm and rubbery in consistency. On section the parenchyma was pink gray and non-crepitant. The left lung was crepitant and emphysematous. Both pleurae were roughened by fibrous adhesions near the apices.

Liver and Biliary System: The liver weighed 2,655 gm. and measured 32 by 24 by 7.5 cm. The external surface was red brown, smooth and glistening and on section the lobular pattern was somewhat accentuated. The portal vein contained no thrombi. The gall-bladder was contracted and contained a large smooth oval-shaped golden yellow calculus measuring 2 cm. in greatest diameter.

Pancreas and Adrenals: These showed nothing of note.

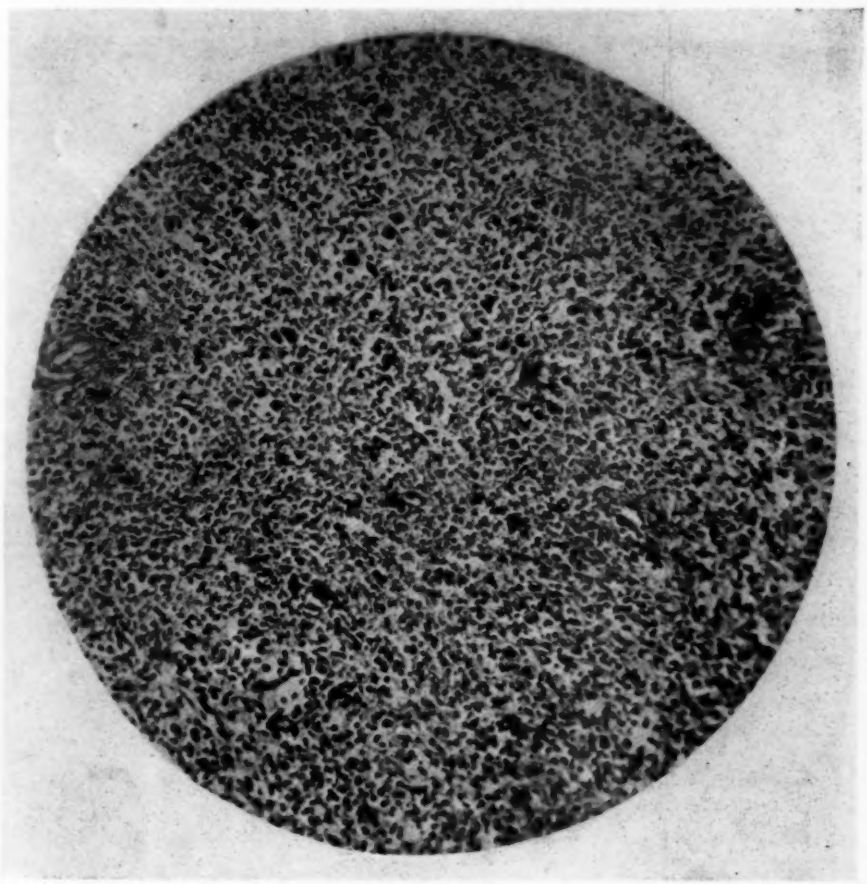

FIG. 3. Photomicrograph of spleen showing fibrosis and numerous Reed-Sternberg cells. H & E × 75.

Kidneys: The kidneys were normal in size but the external surfaces were granular. The capsules could be stripped with ease. Both kidneys presented a normal appearance on section.

Spleen (figure 1): The spleen weighed 820 gm. and measured 19 by 14 by 5 cm. It was firm and meaty in consistency. The external surface was mottled pink red and purple and contained a firm gray white infarct measuring 3.5 by 1.5 cm. near the lower pole. On section the spleen was mottled pink and red. The Malpighian follicles were not seen and the fibrous markings were increased. The pulp could be scraped with difficulty. The splenic vein and artery showed nothing of note.

Lymph Nodes: A careful examination of all the lymph nodes failed to reveal any change in consistency or enlargement of any.

Bone Marrow: Sections from the vertebrae showed the marrow to be grossly abundant and red.

Histologic Examination: Heart: The heart showed a moderate amount of fibrosis.

Lungs: The right lung was completely involved by a lobar pneumonia in the gray hepatization stage. The left lung showed compensatory emphysema.

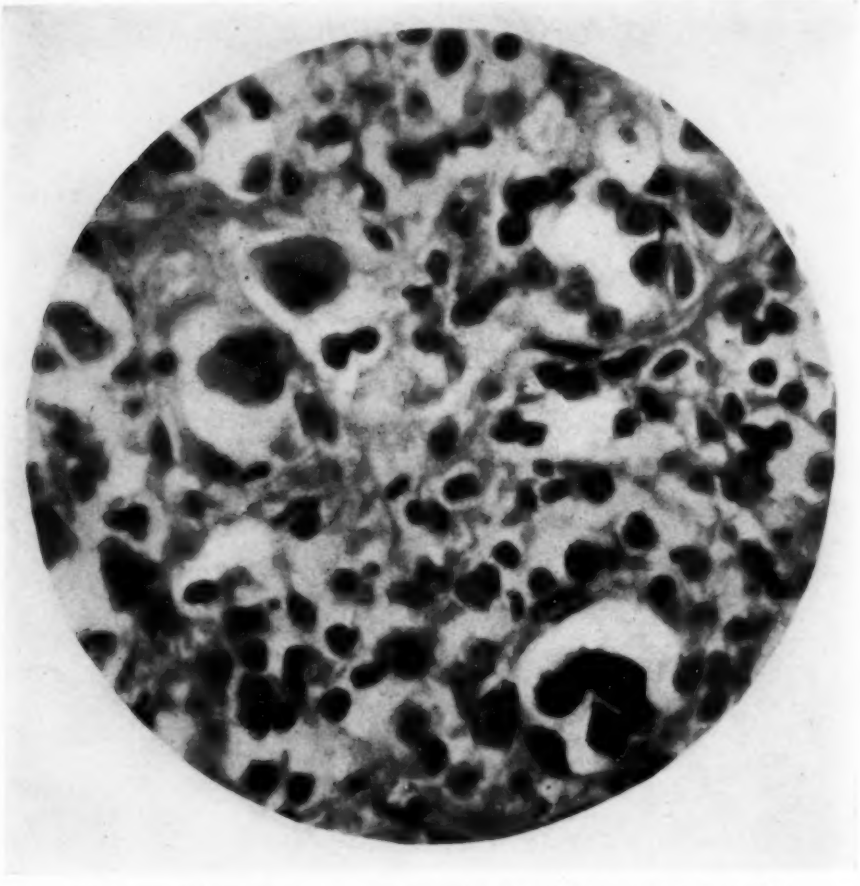

FIG. 4. Photomicrograph of spleen showing details. H & E × 320.

Liver (figure 2): The liver cells were arranged into cords and cords into lobules in an orderly fashion. The sinusoids were all dilated and engorged with blood. Many of them also contained large mononuclear and multinucleated giant cells of the Reed-Sternberg type. The liver cell cords were compressed and many of the liver cells were vacuolated. Almost all contained brown pigment granules.

Pancreas and Adrenal Glands: These showed nothing of note.

Kidneys: Preparations from the kidneys showed benign nephrosclerosis in a moderately advanced stage.

Spleen (figures 3 and 4): The capsule was thickened and the Malpighian corpuscles obliterated. There was an increase in fibrous tissue throughout the spleen

and an infiltration with round mononuclear cells and giant cells some of which were multinucleated while others contained one or two deeply staining nuclei. These latter cells were of the Reed-Sternberg type. One preparation contained a large area of necrotic pale staining splenic tissue. No eosinophiles were seen in the spleen.

Bone (figure 5): Preparations from the vertebrae showed fibrosis of the marrow and infiltration with large cells of the Reed-Sternberg type. A marked increase in eosinophilic cells was also present.

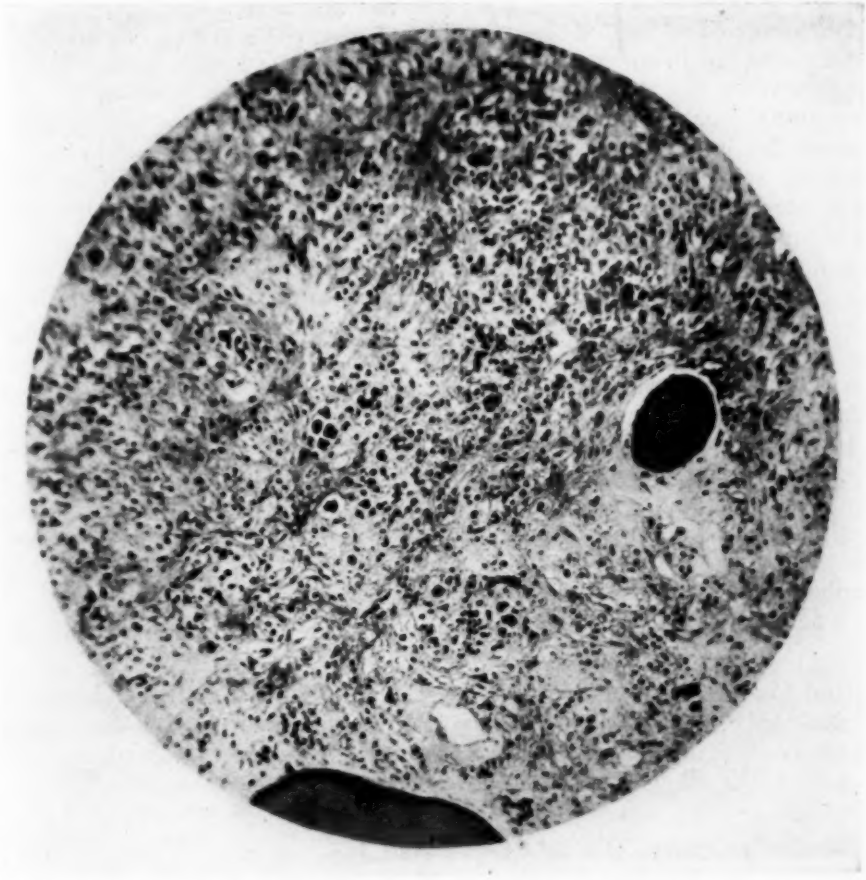

FIG. 5. Photomicrograph of vertebra showing fibrosis, Reed-Sternberg cells, and eosinophiles. The latter are not clear in this black and white picture. H & E × 75.

Anatomic Diagnosis: Hodgkin's disease in spleen and bone marrow; pneumonia, diffuse, right; emphysema in lung, left; congestion of viscera; myofibrosis cordis; fatty changes in liver; nephrosclerosis; fibrous pleural adhesions; cholecystitis; cholelithiasis, chronic.

DISCUSSION

It is impossible completely to rule out lymph node involvement in this case as well as in previous cases. To do so would necessitate serial sections of all the lymph nodes in the body, an obviously impossible task. Short of that, an ex-

ceedingly careful search was made of every available lymph node, superficial or deep, but none showed any alteration in size or consistency. It is felt, therefore, that this is a true case of primary splenic Hodgkin's disease.

Hodgkin's disease should no longer be regarded as "a disease of lymph nodes," as every medical author describes it, but rather as a disease of the reticulo-endothelial system. The involvement is at first local, and then generalized. Accordingly, the lesions may be found wherever this system exists; in the lymph nodes, spleen, liver or bone marrow.

Gebauer [9] in making the clinical diagnosis of primary splenic Hodgkin's disease stressed the following criteria: (1) Enlarged spleen and liver. (2) Pel-Ebstein fever. (3) Weight loss. (4) Blood picture. The latter comprises severe anemia, leukopenia, thrombocytopenia and lymphocytosis. The anemia is so severe that in the four previous cases proved at autopsy,[6, 7, 8, 9] and in ours, the presenting symptoms were weakness, dyspnea and ankle edema and the hemoglobin determinations in all cases were between 25 to 35 per cent. Furthermore, this anemia responds poorly, if at all, to blood transfusions and hematinics. In the generalized form of Hodgkin's disease the anemia seldom approaches this severity. The generalized form is frequently characterized by leukocytosis and eosinophilia and depression of the platelets is not seen. Marked leukopenia and lymphocytosis is the rule in the primary splenic form, and eosinophilia has not yet been described in the peripheral blood smears. There is distinct thrombocytopenia. All these changes are doubtless due to bone marrow involvement.

In the differential diagnosis Gebauer lists leukemia, sepsis, miliary tuberculosis, typhus fever, brucellosis, malaria and hemolytic icterus. Since these are readily ruled out, a diagnosis of primary splenic Hodgkin's disease can be established by exclusion. An aid suggested by Velasco Montes [10] is splenic puncture, which, according to him, is a simple, harmless procedure. The presence of Reed-Sternberg cells and eosinophiles establishes the diagnosis.

Conclusions

Hodgkin's disease is a disease of the reticuloendothelial system and not of the lymphatic apparatus alone. Primary splenic Hodgkin's disease is a distinct entity and can be clinically diagnosed once its existence is generally realized.

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CARCINOMA OF THE PANCREAS WITH PULMONARY LYMPHATIC CARCINOMATOSIS SIMULATING BRONCHIAL ASTHMA: CASE REPORT *

By CHARLES F. SWEIGERT, Lt. Col., M.C., EDWARD F. MCLAUGHLIN, Lt. Col., M.C., and ERLE M. HEATH, Capt., M.C., *Lincoln, Nebraska*

SEVERAL reports in the recent literature [1, 2, 3] have stressed the appearance of asthmatic symptoms as a manifestation of pulmonary metastases from abdominal neoplasms. Mendeloff [1] presented two cases with severe asthmatic dyspnea as the sole manifestation of generalized endolymphatic carcinomatosis. A case of carcinoma of the pancreas with metastasis to the lungs which had been clinically treated as bronchial asthma was described in the case records of the Massachusetts General Hospital.[2] Denenholz and Cheney [4] mentioned a case under observation for coccidioidomycosis or tuberculosis in which, although asthma was not reported, the dominant clinical features were respiratory. Wu [5] studied a series of 49 cases of "lymphangitis carcinomatosa" selected from the literature. It is felt that the following case report of carcinoma of the pancreas with lymphatic metastasis to the lungs will serve further to emphasize the association of respiratory symptoms with cancer arising elsewhere in the body.

CASE REPORT

A 22 year old white male was admitted to the Regional Hospital on April 24, 1945 complaining of pain in the right upper quadrant of the abdomen of six weeks' duration, paroxysmal dry cough of two months' duration, and a loss of 15 to 20 pounds over a two months' period.

History: The past medical, personal and family history were essentially negative. Prior to induction into the Army he had been a student. He had had no foreign service and no previous serious illness.

The patient felt well until about March 15, 1945, at which time he noted the gradual onset of dull, burning epigastric pain. This consisted of a dull sensation of soreness, more marked about one to one and one-half hours after eating. It was aggravated by sudden jarring movement and relieved by doubling up into a jack-knife position but not by taking food. He was hospitalized originally at a satellite station hospital on March 28, 1945. At that time he had some tenderness in the epigastrium but no palpable mass. A flat plate of the abdomen showed no gas beneath the diaphragm and a barium series showed a wide duodenal loop (figure 1) but was otherwise negative. Laboratory findings showed a normal red and white blood count and urinalysis. Stool examination was negative for blood on two occasions; icteric index was 5 on both April 3 and April 19, 1945. Sedimentation rate was 19 mm. per hour. Kahn test was negative. Serum amylase was reported as 800 mg. of re-

* Received for publication November 20, 1945.

ducing sugar produced per 100 c.c. of blood, on April 4; 533 mg. on April 5; and 320 mg. on April 17, 1945. On a bland, low-residue diet the epigastric pain subsided about April 10, 1945. About April 14, however, he developed a pain in the right

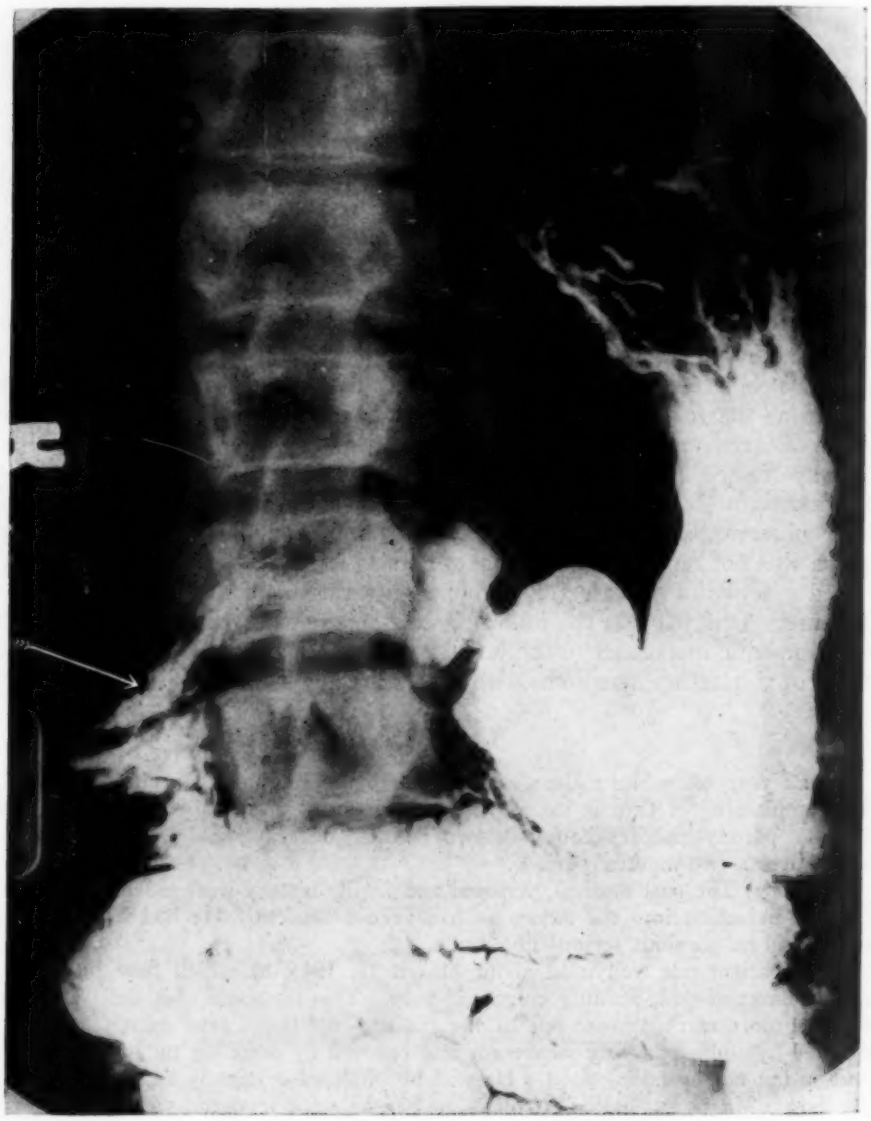

FIG. 1. Showing widening of duodenal loop.

upper quadrant of the abdomen. This was rather steady and deep with no radiation and was relieved only by the jackknife position or by codeine. It was quite severe in intensity and unrelated to food. No definite diagnosis was made at this time, and the patient was transferred to Regional Hospital, Lincoln, Nebraska, April 24, 1945, for further observation.

Physical Examination: At the time of admission the patient had a slight yellowish tint to the sclera and skin. He was thin and apparently dehydrated. Examination of the lungs revealed a few fine and sibilant râles at both bases. The cardiovascular system was normal. The abdomen was flat and fairly rigid throughout the entire

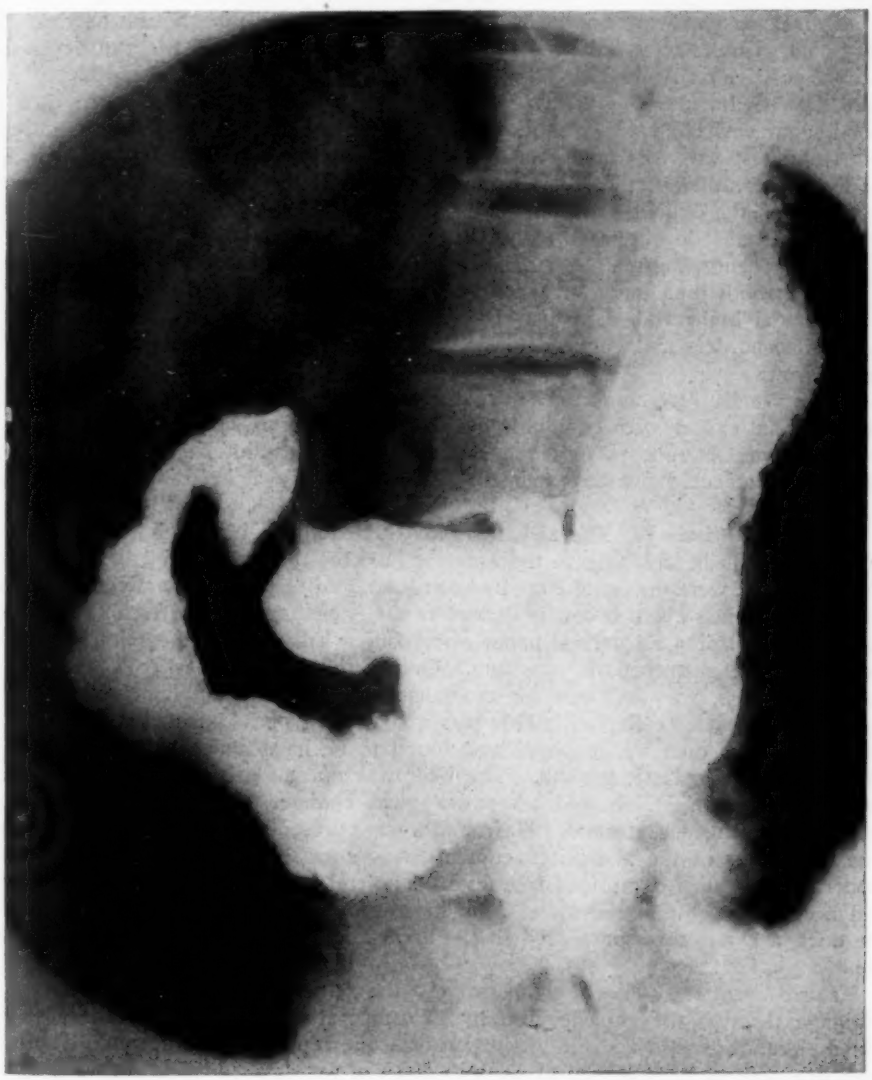

FIG. 2. Showing apparent defect of lesser curvature of stomach.

upper portion. There was definite localized tenderness in the right upper quadrant about 4 to 6 cm. to the right of the midline. There were no definite palpable masses at this time, but there was a sense of resistance in the right upper quadrant.

Course: After admission his pain remained unchanged and required codeine and aspirin for relief. He was observed frequently to sit in bed in a jackknife position so that his knees were doubled up onto his abdomen. He stated that this gave him

some relief from the pain. Icterus became progressively more marked and by April 27 the patient was clinically jaundiced. On April 28, for the first time, a firm, irregular, tender mass not well outlined, was palpable in the epigastrium. At this time asthmatic wheezes were heard diffusely over the chest, especially on the right side. Laboratory findings at this time were as follows: Urinalysis was negative; urobilinogen urine test was positive in dilution 1:2, on April 30. Serum amylase was 180 Somogyi units on April 20. The icteric index was 29, and the van den Bergh a direct positive on April 26. The white blood count was 6,300, and red blood count 5,120,000. Sedimentation rate was 30 mm. on April 26, and 46 mm. on April 30. Blood sugar was 125 mg. per cent. Blood chlorides were 439 mg. per cent on April 30. Kahn test was negative. Gastrointestinal series revealed a constant defect of the lesser curvature of the stomach which was visible when the patient was turned about 70° in the oblique position (figure 2). There appeared to be some widening of the duodenal loop (figure 1).

Chest roentgenogram on April 30, 1945 (figure 3) showed a dissemination throughout both lung fields of a definite infiltrating increased density. This was a peribronchial infiltration more marked at the hilar regions but also extending along the cardiac borders and outward toward the periphery of the lungs. No portion of the lungs was spared.

Preoperative Impression: The preoperative impression was that this patient had an abdominal cancer with lymphatic metatasis to the lungs. The most probable site of tumor was thought to be the pancreas although an intrinsic neoplasm of the digestive tract could not be excluded. An exploratory laparotomy was performed May 5, 1945.

Operative Findings: The abdomen was opened through a high right rectus incision and immediately beneath the anterior parietes the pyloric end of the stomach and duodenum were encountered. Beneath them and displacing them forward was a nodular firm mass about 8 cm. in diameter. It extended and tapered off to the left, apparently replacing all normal pancreatic tissue. Enlarged hard lymph nodes were palpated in the gastrohepatic omentum. One of these, together with a section from the tumor mass, was removed for examination. The common duct was distended and the gall-bladder collapsed. This was a somewhat paradoxical finding, explained when the cystic duct was exposed and found to be hard and contracted due to infiltration by a neoplastic growth. The liver was normal in size and not grossly involved. The stomach showed no pathological changes. The spleen was slightly enlarged but otherwise normal. Hard nodes were present in the gastrocolic omentum. The remainder of the abdominal contents was normal. The abdomen contained a moderate amount of bile-tinged free fluid. The common duct was opened and probed and a complete obstruction found near its lower end. A T-tube was inserted into the duct, a cigarette drain placed in the area, and the abdominal wall closed about them.

Postoperative Course: Postoperatively the patient's jaundice was relieved by drainage through the choledochostomy. Postoperative management otherwise consisted of relief of pain and the institution of a bile replacement program. The measured drainage of the bile stayed close to 500 c.c. per day. This bile was desiccated and administered in capsule form (7 to 16 capsules daily of approximately 0.65 gram each). This program resulted in return of the stools to normal color and maintenance of an average prothrombin time of 90 per cent of normal without artificial aid. By May 17, 1945, a definite increase of frequency and severity of the paroxysms of cough was noted. The patient also had a progressive increase in pain and by May 30 he had a constant dull pain in the epigastrium, always partially relieved by the jackknife position. The patient's postoperative course was characterized by progressive failure, weakness, pain, increasing respiratory distress and emaciation. At

this time constant diffuse sibilant râles and asthmatic wheezes were heard throughout both lung fields, presenting the clinical picture of severe, intractable bronchial asthma. The patient had frequent severe paroxysms of cough and marked dyspnea and wheezing, plainly audible at a distance. He failed rapidly and died June 14,

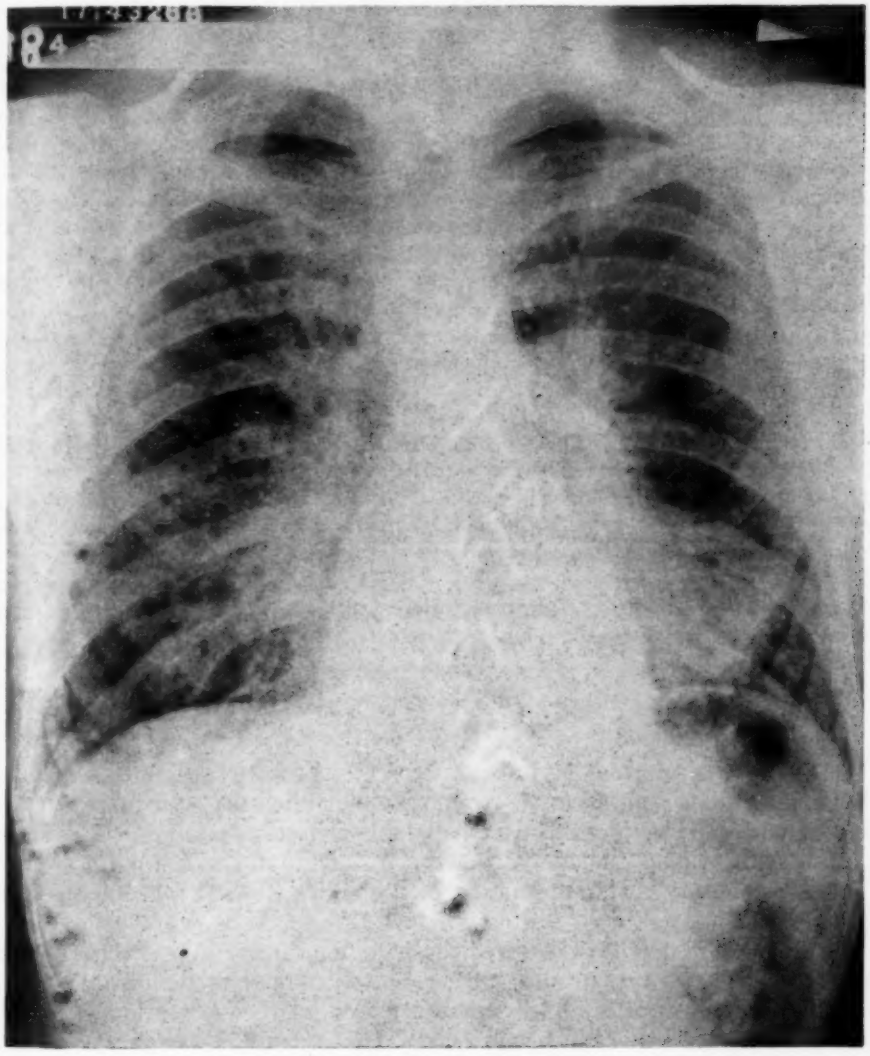

FIG. 3. Showing disseminated infiltrating type of density in the lungs.

1945. The total duration of the illness from the onset of the first symptoms was two months.

Autopsy Findings: At necropsy, marked wasting and jaundice were evident. The abdominal viscera appeared to be normally disposed. However, the pyloric end of the stomach and the duodenal loop were displaced forward by an underlying mass. The lymph nodes at the root of the mesentery and those surrounding the colon were

enlarged and firm. The mass, about 8 by 5 by 5 cm. in size, was located behind the stomach and duodenal loop. A greater portion of the mass lay in the region of the pancreas and along the first portion of the duodenum at the junction of the common bile and pancreatic ducts. No normal pancreatic tissue was found; rather, the pancreas was replaced by a grayish-white homogeneous mass which cut with considerable resistance. The gall-bladder was completely collapsed and slightly thickened. The cystic duct was completely obstructed approximately 1.5 cm. from its junction with the common duct. Distal to the T-tube the common duct was completely occluded and a probe could not be passed into the duodenum. The liver was studded with grayish-white nodules 0.5 to 2.5 cm. in diameter. On the inferior surface of the liver there was a grayish-white extension from the tumor mass. On the external surface of the lungs there were grayish-white linear seedings of discrete, hard, BB-shot nodules. The tracheal, bronchial, and bronchopulmonary nodes were enlarged and firm. The left lower lobe bronchus was almost completely occluded at several points along its course by the enlarged colorless nodes. The lungs cut with a gritty hard sensation. All lung lobes, except the right lower lobe, were consolidated and an abscess cavity 4.5 cm. in diameter was found in the left lower lobe.

Microscopic Report: Microscopic sections of the pancreas consisted almost completely of infiltrating adenocarcinoma. However, some areas were seen to contain an admixture of tumor cells and a few surviving pancreatic acini. All sections of the lungs showed a profuse proliferation of tumor cells with partial obliteration of the normal lung structure. The alveolar spaces were partially lined by infiltrating tumor cells and free tumor cells were seen in many spaces. In the liver there was extensive destruction of the normal hepatic architecture by infiltrating adenocarcinoma. In addition, metastases were noted in the hilar lymph nodes, common bile duct, adrenal glands, stomach and vertebrae. Sections from the brain, heart, gall-bladder, spleen and kidneys were free of metastasis.

Pathological Diagnosis: Carcinomatosis resulting from dissemination of pancreatic adenocarcinoma to the lungs, bronchial lymph nodes, liver, adrenals and vertebrae.

Discussion

This case was unusual in several respects. First, it presented a difficult differential diagnostic problem. Secondly, it illustrates the occurrence of bronchial asthma secondary to pulmonary lymphatic metastasis and the association of the latter with primary abdominal cancer. In addition, the age of the patient, 22 years, is unusual, and the duration of the entire illness (two months) was strikingly brief.

The differential diagnosis involved consideration of several possibilities. The onset with rather marked burning epigastric pain and upper abdominal tenderness along with the defect of the lesser curvature seen on roentgenogram (figure 2) suggested the possibility of a gastric ulcer. The increased serum amylase maintained over a period of several weeks, though not typical of an acute pancreatitis, suggested pancreatic involvement. The age of the patient, the cough, râles and wheezes, and the chest roentgenogram (figure 3) suggested the possibility of either tuberculosis, silicosis, sarcoid or Hodgkin's disease. The progressive development of jaundice focused attention on the biliary system. However, the marked weight loss, the palpable mass, the progressive jaundice, the wide duodenal loop demonstrated roentgenographically, and the pulmonary symptoms and signs, if assumed to be due to one disease process, could be explained only on the

basis of a neoplastic mass in the region of the upper gastrointestinal tract with metastasis to the lungs. The elevated serum amylase and the location of the mass suggested the pancreas as the most likely site of the primary growth. The preoperative diagnosis was: Intra-abdominal malignant growth, probably pancreatic, with lymphatic metastasis to the lungs.

This case differs from those described by Mendeloff [1] in that pulmonary symptoms were not the sole presenting complaints. However, the pulmonary symptoms and signs were sufficiently prominent to play an important rôle in the preoperative diagnosis. In Wu's [5] review of 30 cases of generalized lymphatic carcinomatosis of the lungs the most frequent site of primary tumor was the stomach; others were the breast, prostate, pancreas, intestines, liver, pharynx, gall-bladder, appendix, bladder and rectum. The most marked symptom of carcinomatosis of the lungs is usually progressively severe dyspnea. Paroxysmal dry cough, however, is a frequent symptom and, as in this case, may be the first respiratory symptom noted. These symptoms, when accompanied by marked weight loss, anorexia and other nonspecific manifestations of malignancy, should suggest the possibility of pulmonary carcinomatosis. Roentgenograms are suggestive of this, although not conclusive. Similar findings may occur in silicosis, miliary tuberculosis, pulmonary fibrosis, coccidioidomycosis and the lymphomata.

The method of spread to the lungs is generally thought to be a direct extension along the lymphatics. Greenspan [6] described the effect of carcinomatous lymphangitis on the production of obliterative endarteritis with resultant right heart failure. Schattenberg and Ryan [3] reported some observations which support the possibility that some tumor cells may gain entrance to the venous circulation through the thoracic duct. The postmortem pathology of these patients has been adequately described by Schattenberg and Ryan.[3]

As to the surgical care of this patient, it would have been desirable, in view of such apparent widespread malignancy, to have avoided laparotomy. However, because of the increasing and distressing jaundice and because the exact nature of the intra-abdominal lesion was not definitely established, it was felt that laparotomy was indicated. Because of the extensive neoplastic involvement, definitive surgery was out of the question. Cholecystoenterostomy would have been desirable but because the cystic duct was involved in the malignant process and completely obstructed, this could not be done. External biliary drainage, using a T-tube in the common duct was the only practicable procedure. When cancer is so rapidly spreading and overwhelming, surgery, of course, has little to offer except to assist in establishing the diagnosis and to provide palliative measures for the relief and comfort of the patient. The extent of the process in this patient was evidenced preoperatively more by the chest findings and the roentgenograms than by the local abdominal findings.

Summary

A case of carcinoma of the pancreas with lymphatic metastasis to the lungs is presented along with a brief discussion of the symptomatology, differential diagnosis, and pathogenesis. The clinical features of this case emphasize the need of considering carcinomatous metastases as a cause of asthmatic symptoms and diffuse pulmonary infiltrations.

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COMPLETE TRANSPOSITION OF THE ARTERIAL TRUNKS WITH CLOSED INTERVENTRICULAR SEPTUM *

By JAMES W. MCELROY, Major, M.C., JOHN P. DAVIS, Major, M.C., and ROBIN P. MICHELSON, Captain, M.C., A.U.S., *Camp Gordon, Georgia*

SINCE Abbott's [1] clinical classification of congenital anomalies of the heart, much interest has been manifested in the diagnosis and specific anatomical defects of these conditions. On a clinical basis she has classified these anomalies into three great groups, as follows: (1) Acyanotic group—cases without abnormal communication between the two sides of the heart, (2) cyanosis tardive group—cases of arterial-venous shunt with transient or terminal reversal of flow, and (3) cyanotic group—cases of venous-arterial shunt. It is the latter, the cyanotic group, into which the anomaly of transposition of the great vessels falls. Since our discussion will be concerned mainly with this anomaly, space will not permit enumeration or description of the other anomalies of this group.

Transposition of the arterial trunks refers to an abnormal relationship in the origin of the aorta and pulmonary artery. The degree of transposition depends primarily upon the stage at which normal embryonal development is interrupted, as is basically true of all congenital heart anomalies. Abbott [1] in an analysis of 1,000 cases classifies this anomaly as follows: (1) Dextro-position of the aorta, in which this vessel arises from a position to the right of the normal, viz., from the left ventricle (with intact septum), from both ventricles (overriding a septal defect), or from the right ventricle with a double conus, (2) partial transposition, in which both arterial trunks arise from the same ventricle, (3) corrected transposition, in which the aorta and pulmonary artery are in abnormal relation to each other, yet arise from their proper ventricles, and (4) complete transposition (also called crossed transposition), in which the aorta arises from the right ventricle and the pulmonary artery from the left ventricle.

Of 1,000 cases of congenital heart disease analyzed by Abbott [1] complete transposition of the great arterial trunks was the primary defect in 49, of which 32 had closed ventricular septa and 17 had ventricular septal defects.

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Complete transposition of the arterial trunks is always associated with another anomaly, permitting communication between the right and left sides of the heart, for otherwise blood of the systemic circulation could not become oxygenated. There are three anatomical openings which permit passage of blood between the two sides of the heart and occur singly or in combination. These openings are: interauricular septal defect, interventricular septal defect, and communications between the aorta and pulmonary artery (usually patent ductus arteriosus). Kato [2] reviewed the cases of complete transposition reported in the literature prior to 1929 and discovered 92 such cases, to which he added five of his own. This series of 97 cases we have reviewed in table 1, which reveals the relative frequency of the various combinations of anatomical openings between the two sides of the heart occurring in combination with complete transposition of the great vessels.

TABLE I

Analysis of 97 Cases of Transposition of the Arterial Trunks Reviewed by Kato,[2] to Show the Relative Frequency of Associated Anomalies

Transposition of the Arterial Trunks		
1. Closed ventricular septum, occurring		50
a. alone	0	
b. with patent foramen ovale	12	
c. with patent ductus arteriosus	9	
d. with patent foramen ovale and ductus arteriosus	27	
e. with pulmonary artery arising from aorta	1	
f. with pulmonary artery arising from aorta with patent ductus arteriosus	1	
2. Open ventricular septum, occurring		45
a. alone	12	
b. with patent foramen ovale	19	
c. with patent ductus arteriosus	5	
d. with patent foramen ovale and ductus arteriosus	9	
3. Data insufficient		2
Total		97

In 86 cases of this anomaly reviewed by Kato [2] in which the age was stated, the maximum age at which death occurred was 56 years. The average length of life was 2.3 years; however, since only four patients lived longer than four years (56, 21, 21, and 19 years), a more representative average of 7.8 months is obtained by omitting these four cases.

The symptomatology is variable. There may be observed no symptoms, especially in those patients who succumb after a few days or weeks of life. On the other hand, any one or more of the symptoms occurring in congenital heart disease may be encountered, especially those of the respiratory, cerebral, and gastrointestinal systems. Of these, the most frequently encountered are dyspnea, convulsions, anorexia, and regurgitation of food. Of the physical findings, cyanosis is by far the most common and is almost invariably present except in early infancy when it may be absent. Cyanosis is usually aggravated by exertion, such as occurs with crying or feeding. Clubbing of the digits is frequently present in patients who survive for longer than a few weeks. The heart is usually enlarged, especially the right ventricle, as may be shown by roentgen examination and by an abnormal right axis deviation of the electrocardiogram. Murmurs and thrills are not constant findings, and when present are dependent upon an accompanying

septal defect or patent ductus arteriosus. Of 49 cases of complete transposition analyzed by Abbott,[1] 19 presented murmurs; of the 32 cases with intact ventricular septa systolic murmurs were present in eight, and of the 17 cases with interventricular septal defects systolic murmurs were found in 10 and a double murmur in one.

The diagnosis of complete transposition of the arterial trunks is rarely made except at autopsy. Taussig [3] in 1938 called attention to four ante-mortem findings the combination of which she considered to be characteristic of this condition: (1) Persistent cyanosis, (2) cardiac enlargement, especially of the right ventricle, (3) narrow aortic shadows in the antero-posterior roentgenogram, and (4) an increase in the width of the roentgenographic shadow of the great vessels in the anterior oblique position.

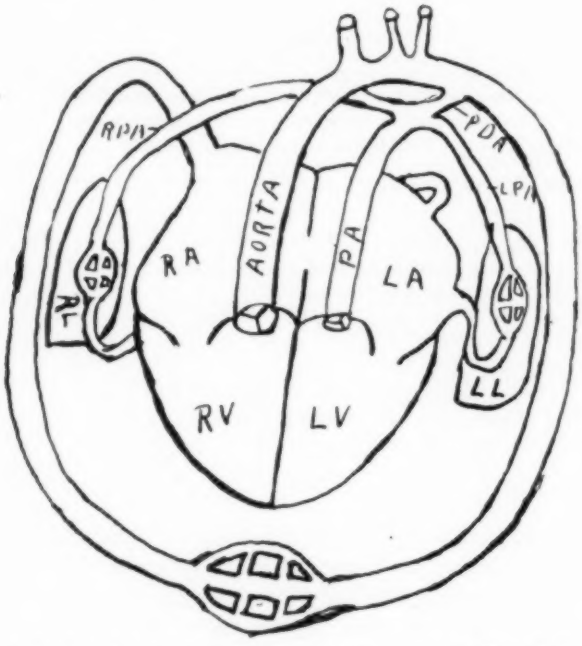

FIG. 1. Schematic drawing representing complete transposition of the arterial trunks with patent foramen ovale and ductus arteriosus. R.A., right auricle; L.A., left auricle; R.V., right ventricle; L.V., left ventricle; P.A., pulmonary artery; R.P.A., right pulmonary artery; L.P.A., left pulmonary artery; P.D.A., patent ductus arteriosus; R.L., right lung; L.L., left lung. (Reproduction by U. S. Army Signal Corps.)

CASE REPORT

A white male infant, the second of uniovular twins, was born May 15, 1945 at 7:44 a.m. The first-born twin, also a male, was delivered at 7:35 a.m. on the same date. Both were full term and were delivered by version and breech extraction without difficulty. The duration of labor was 24 hours. The common placenta and the cords were of normal appearance.

The first-born twin weighed six pounds and 13 ounces (3.1 kg.) at birth and was never noted to be cyanotic. Examination prior to discharge from the hospital on May 28, 1945 revealed no abnormalities. During routine examination at age four

weeks a loud, blowing, systolic murmur at the base of the heart was heard. An electrocardiogram made that date was normal. At age two months the infant was seen by the parents to suddenly become cyanotic and die within two hours. Just before death the infant was examined by the resident pediatrician of a nearby hospital, who

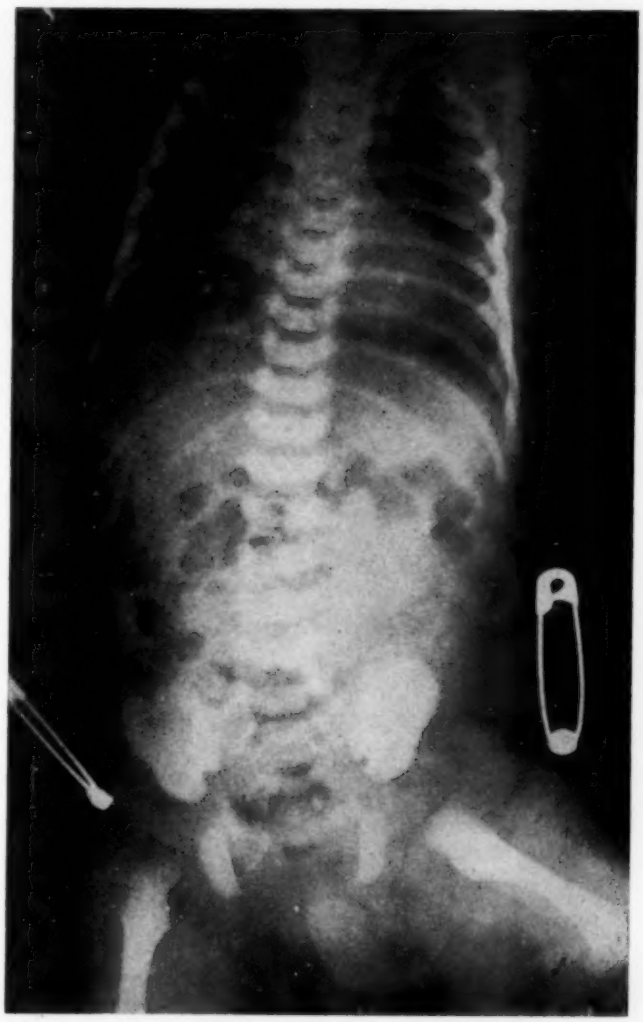

FIG. 2. Roentgen-ray made at age one day showing the size of the heart. (Reproduction by U. S. Army Signal Corps.)

expressed the opinion that death was due to acute cardiac failure. Permission for autopsy was refused.

Both parents were healthy and blood Kahn reactions for syphilis were reported as negative. There was no history suggestive of congenital heart disease in the family. This was the mother's first pregnancy.

The last-born twin, the subject of this report, weighed six pounds and five ounces (2.87 kg.) at birth and was noted to be moderately cyanotic, the color varying in

intensity with exertion or crying. There was noted no stridor, dyspnea, or convulsive seizures. The infant was bottle-fed and developed normally except for varying degrees of cyanosis. On June 1 examination revealed a fairly well-nourished, moderately cyanotic infant. Examination of the heart revealed no enlargement, thrills, abnormal sounds or accentuations, murmurs, or arrhythmias. The clinical chart indicated that the infant continued to gain weight and showed no significant change until June 12, when a more severe attack of cyanosis prompted the administration of oxygen by B–L–B mask. At 4:15 p.m. on June 22 respirations became slow and weak, the lungs were normal, and the lower border of the liver was palpated 5 cm. below the right costal margin. Coramine, oxygen, and artificial respiration were administered before death, which occurred at 4:55 p.m. on June 22, 1945.

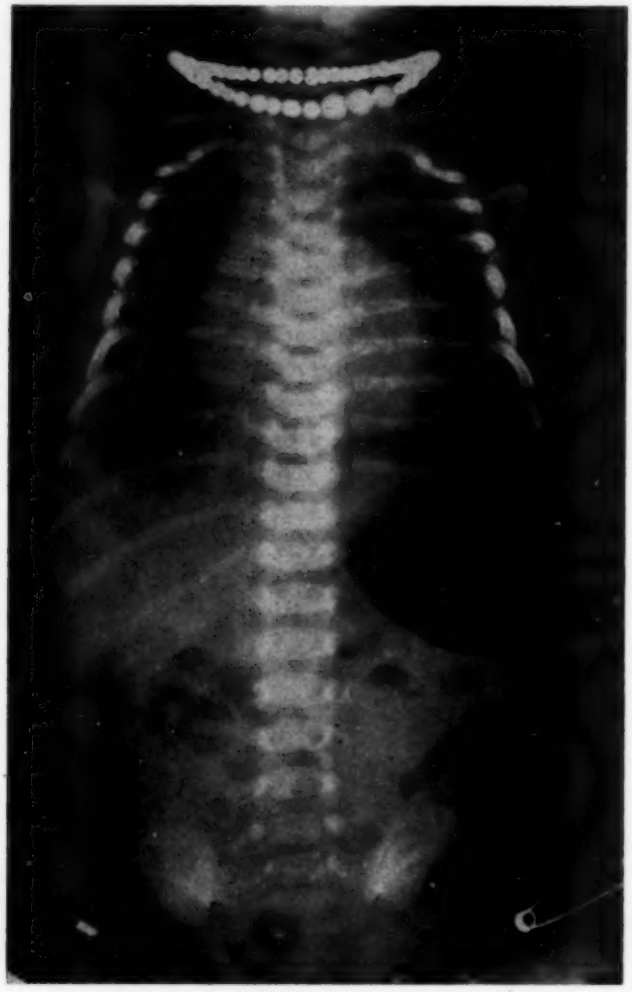

FIG. 3. Roentgen-ray made at age one month showing contour and enlargement of the heart. (Reproduction by U. S. Army Signal Corps.)

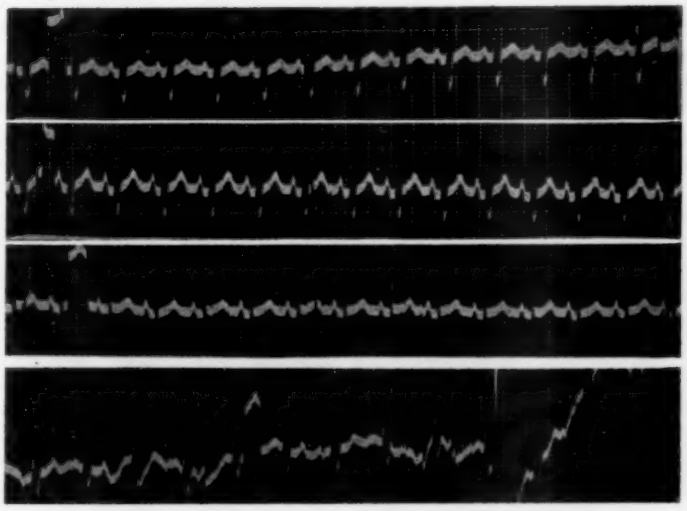

FIG. 4. Electrocardiogram made at age two weeks showing right axis deviation. (Reproduction by U. S. Army Signal Corps.)

FIG. 5. Photograph of the heart: Right ventricle opened, with probe in aorta arising from right ventricle. (Photo by U. S. Army Signal Corps.)

Laboratory and Special Examinations: On May 20 the blood showed hemoglobin 18 gm. (Sahli), red blood cells 5,800,000, white blood cells 6,100, with neutrophiles 40 per cent, lymphocytes 55 per cent, and eosinophiles 5 per cent.

Roentgen examinations of the chest showed normal lung shadows and progressive enlargement of the heart, which presented a globular appearance. The cardio-thoracic ratio showed the following changes on successive films: 56 per cent on May 16 (figure 2), 59.2 per cent on May 28, and 61 per cent on June 16 (figure 3).

FIG. 6. Photograph of the heart: Left ventricle and auricle opened, with probe in patent foramen ovale. (Photo by U. S. Army Signal Corps.)

An electrocardiogram (figure 4) made on June 1, 1945 revealed the following: The tracing showed a definite right axis deviation, the QRS complexes in Leads I and II being of the N type, with S_1 slightly greater than R_1, while S_2 and R_2 were equidistant. The main deflection of QRS_3 was up. There was regular sinus rhythm; the rate was 140 per minute. The P waves were of normal duration, size and contour. The S–T–T combinations showed no abnormalities. Interpretation: Sinus tachycardia and right ventricular preponderance, compatible with the clinical diagnosis of congenital heart disease.

Autopsy Examination: General: The body was that of a well developed, well nourished, white male infant appearing about the stated age of five weeks. The head, neck, thorax, abdomen, and extremities were normal. The skin showed a marked degree of cyanosis, and postmortem lividity and rigor mortis were fairly well developed. The infant weighed 7 pounds and 5 ounces (3.64 kg.). Primary incision: An incision was made from the suprasternal to the xiphoid notches, and the autopsy was limited to the thorax. The rib cage was lifted off in the usual manner and the pleura inspected. No adhesions were found. The left pleural cavity contained 50 c.c. of yellowish serous fluid. Heart and lungs: The heart and lungs were removed in mass: Both lungs were edematous and on cut surface oozed frothy fluid. No areas of consolidation, hemorrhage, or infarction were found, although in the dependent portions there was some atelectasis. The heart was enlarged. The pericardial sac appeared normal, being free of fluid and adhesions. The overall measurements of the heart were 6 cm. by 5 cm. by 3 cm. The wall of the left ventricle measured 5 mm. in thickness, and that of the right measured 4 mm. The coronary system appeared normal. The aorta arose from an enlarged right ventricle (figure 4) and communicated with the pulmonary artery through a very wide patent ductus arteriosus. The pulmonary artery arose from the left ventricle and branched into both lungs. Both vessels were guarded by a three-cusp semilunar valve. The right ventricle appeared to be markedly enlarged and the wall thickened. The left ventricle was of normal size and the chamber was smaller than the right. The auricles and the atrioventricular valves appeared normal. The foramen ovale was fully patent (figure 5) and measured about 3 mm. in diameter. The interventricular septum was intact.

Histological Examination. Lungs: Sections of the lungs showed scattered areas in which the alveoli had not expanded. In other areas where the lung was fully expanded the septal capillaries were markedly engorged. There were numerous hemosiderin-bearing macrophages among the cells lining the alveolar sacs and within the septa. Heart: Microscopic sections of the heart showed normal epicardium with the usual covering of mesothelial cells and a myocardium composed of the normal branching syncytium of striated muscle. The endocardium appeared normal. Cause of death: Acute congestive heart failure, due to congenital cardiac disease, with transposition of the aorta and pulmonary artery, patent ductus arteriosus and patent foramen ovale.

Comment

This case represents an instance of complete transposition of the arterial trunks with closed intraventricular septum, patent foramen ovale and patent ductus arteriosus. The only significant ante-mortem findings were persistent cyanosis, progressive enlargement of the heart and marked right axis deviation of the electrocardiogram. A clinical diagnosis of congenital heart disease of the cyanotic group was made, but the exact anatomical defects were not determined until autopsy.

At autopsy considerable interest was manifested by the staff in the probable course taken by the circulation in this condition (figure 1). In 1850 a case identically similar to ours was described by Johnson,[4] who proposed that the direction of blood flow occurs as follows: Venous blood enters the right auricle, a greater portion of which passes into the right ventricle to be expelled into the aorta and the systemic circulation. However, this being unoxygenated blood, in order to maintain life for longer than a few minutes, a certain amount of blood must reach the lungs for aeration and does so by passage from right to left auricle through the patent foramen ovale, while at the same time a portion of aerated blood passes

from the pulmonary artery through the patent ductus arteriosus into the systemic circulation. On the other hand, there is much evidence to discredit this assumption. More recent literature supports the belief that the direction of blood-flow is from the aorta to the pulmonary artery through the patent ductus arteriosus and from the right to the left auricle through the patent foramen ovale. Most writers, including Abbott and Dawson,[5] who cite a similar case of Pappenheimer's, agree with the latter theory on the basis of experimental evidence that the pressure is greater in the aorta than in the pulmonary artery. Uhley [6] in 1942 pointed out that the most important factor in the flow of blood from the left to the right auricle in cases of interauricular septal defect is the effect of gravity, the right auricle being situated beneath the left, and the septum lying more or less horizontally.

Whatever may be the mechanism of blood-flow which actually occurs in this arrangement of cardiac anomalies, the causes of cyanosis are clearly described by White [7] as being dependent upon three factors: (1) Mixture of venous and arterial blood wherein the venous blood is at least 30 per cent of the total and thus passes the threshold for cyanosis, (2) dilatation of the capillaries of the skin and mucous membrane accompanying the slowing of the peripheral blood, and (3) insufficient oxygenation of the blood in the lungs.

That an autopsy on the twin of this infant was not performed is regrettable. Inasmuch as it is likely that congenital heart disease also existed in that infant, the comparison of the possible anomalous lesion or lesions with those of its identical twin might have been of considerable interest.

Summary

1. A case of complete transposition of the arterial trunks, associated with patent foramen ovale and ductus arteriosus is presented and discussed.

2. This combination of anatomical defects is relatively rare, occurring 27 times in 97 cases of complete transposition of the arterial trunks analyzed by Kato.[2]

3. The theories regarding the direction of blood-flow have been presented and discussed.

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6. Uhley, M. H.: Lutenbacher's syndrome and a new concept of the dynamics of interatrial septal defects, Am. Heart Jr., 1942, xxiv, 315–328.
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EDITORIAL

ACQUIRED RESISTANCE TO ANTIBIOTICS

It has long been recognized that microörganisms may acquire a marked degree of resistance to a drug as a result of exposure to sublethal concentrations, although originally they were highly sensitive to its action. This phenomenon was first brought to general notice by Ehrlich nearly half a century ago in his studies of the action of arsenicals in spirochetal and trypanosomal infections. He applied the term drug-fast to such resistant strains.

In the more recent past many similar observations have been made with respect to the sulfonamides. Many highly susceptible species of organisms, such as the pneumococcus, the streptococcus and the gonococcus, have been found capable of acquiring such resistance, often with disconcerting rapidity. This is also true of the antibiotics penicillin and particularly streptomycin.

This resistance may be produced artificially in the laboratory by cultivating the organisms in media containing suitable concentrations of the drug. It may also develop during the course of an infection in animals or in man if the drug is given in inadequate doses or particularly if its administration is interrupted or carried out in an irregular haphazard fashion. In many cases failure to cure an infection has been shown to be associated with the development in the body of resistance to the drug by the infecting strain of the microörganism. As a rule such drug-fast strains do not differ in any other conspicuous or significant way from the strain in its original sensitive state. Its virulence is usually unimpaired. Once acquired, the resistance appears to be maintained indefinitely both in laboratory cultures and in the body.

Very little is known as to the mechanism of the antibacterial action of these drugs, although it has been assumed that they interfere with some vital metabolic activity in such a way as either to kill the cell or at least to prevent its growth and multiplication. Even less is known of the changes which render the organism resistant. It is an interesting and practically important fact, however, that acquired resistance to either the sulfonamides, penicillin or streptomycin does not affect the original susceptibility of the strain to the other drugs. The precise mechanism or site of their action is evidently different.

There are two obvious ways in which a strain of organisms might become resistant. Exposure to a sublethal concentration of the drug might bring about an adaptation as the result of a gradual progressive change in the metabolic activities of the bacterial population as a whole. This might, on the other hand, operate by killing or inhibiting the growth of the sensitive individuals and permit a few initially resistant organisms to outgrow and replace the others. The former hypothesis seems inherently improbable because of the great rapidity with which a strain may become resistant, even

within 24 hours in the case of one *H. influenzae* strain.[1] Recent investigations to determine this point have furnished strong direct evidence in favor of the latter alternative.

Alexander and Leidy [1] have reported careful studies of 14 strains of Type b *Hemophilus influenzae* derived from human infections, with respect to their sensitiveness to streptomycin. All the strains initially were sensitive to streptomycin, growth being inhibited by from one to 13 units per c.c. of medium when ordinary inocula containing from 1 million to 1700 million organisms were used. Ten patients recovered under treatment, but four did not respond to streptomycin. In three of these cases, subsequent cultures yielded strains which were resistant to this drug, growing well in media containing 1000 units per c.c.

They searched for individual organisms which were resistant to streptomycin in 10 of the initial (sensitive) strains by inoculating large quantities (142 billion to 522 billion organisms) on media containing 1000 units of streptomycin per c.c. In every case a small number of colonies of resistant organisms appeared, the incidence varying from about 1 : 1 billion to 1 : 14 billion organisms. There was no correlation between the relative number of resistant organisms found in the original cultures and the subsequent development of drug-resistance during treatment. The relative number of colonies of resistant organisms seemed to depend principally upon the size of the original bacterial population cultured. Patients with severe infections and relatively large numbers of organisms in their tissues would therefore be more likely than those with milder infections to harbor a sufficient number of drug-resistant organisms to overgrow the others and produce a resistant strain.

Miller and Bonnhoff [2] have reported similar studies of 18 strains of meningococci which were sensitive to streptomycin. By making large inocula on media containing streptomycin, they obtained (in 16) a few colonies of two different types of streptomycin-resistant organisms. One type closely resembled the original strain except in its resistance to streptomycin. The other differed in growing only on media containing streptomycin. It was avirulent for untreated mice, but if the mice were treated with streptomycin, it acquired virulence and the animals succumbed to the infection.

The source of the few initially resistant organisms in these cultures is a matter of interest. Alexander and Leidy [3] have advanced evidence to show that they possess the characteristics of bacterial mutants. Thus, there is a marked variation in the number of resistant individuals in different cultures of the same strain, depending upon how early in the growth of the culture the first resistant mutants happened to appear. The calculated rate of oc-

[1] ALEXANDER, H. E., and LEIDY, G.: Mode of action of streptomycin on Type b *H. influenzae*. I. Origin of resistant organisms, Jr. Exper. Med., 1947, lxxxv, 329–337.

[2] MILLER, C. P., and BONNHOFF, M.: Development of streptomycin-resistant variants of meningococcus, Science, 1947, cv, 620.

[3] ALEXANDER, H. E., and LEIDY, G.: Mode of action of streptomycin on Type b *Hemophilus influenzae*. II. Nature of resistant variants, Jr. Exper. Med., 1947, lxxxv, 607–621.

currence of resistant individuals is very low, about 1/20 billion per bacterium per bacterial generation, and it was relatively constant for the different strains. The trait was transmitted unchanged through many generations. Miller and Bonnhoff concur in regarding their variants as mutations. It is, in fact, difficult to conceive of any other explanation for the origin of the strains of meningococci which required streptomycin for their growth.

Demerec [4] also concluded that the development of resistance to penicillin by staphylococci was the result of a mutation, since the variation in the number of resistant bacteria in samples from different cultures was much greater than in different samples from the same culture. In this case, however, he had to assume a consecutive series of mutations to explain the more gradual, steplike increase in resistance which he observed.

These observations have important practical implications. Clinical observations indicate that drug-resistance is more likely to appear in patients who are inadequately treated than in those whose treatment is efficient. Accepting the hypothesis that the resistant organisms are mutants, this observation may be explained in part by the fact that in well treated patients the multiplication of the sensitive organisms is promptly stopped and there is a smaller bacterial population from which resistant mutants might arise. There is reason to believe that the outcome depends in part upon the number of such resistant organisms present. It is probably rare that a single organism, however virulent, can initiate a progressive infection; an appreciable even if relatively small number are required. In an adequately treated patient the number of resistant organisms may be kept below that required for an adequate infecting dose, and these may then be disposed of by the natural defensive forces of the body.

The development of drug-resistant strains of organisms, however brought about, is most unfortunate, both for the individual who may succumb to the infection and from the standpoint of public health. Such resistant strains are likely to be disseminated, and as a result of natural selection they are likely gradually to replace the sensitive strains. That this may be happening is indicated by evidence which suggests that sulfonamide-fast strains of gonococci are being observed clinically with increasing frequency. The fight against infectious disease may develop into a race between man with his efforts to discover new and better antibiotics, and the microörganisms with their capacity to develop mutant forms which are resistant to the new drugs.

Another point of practical significance is the fact that organisms which become resistant to one antibiotic retain their original sensitiveness to others. This makes it rational to administer them in combination when it is feasible to do so. The few variants of *H. influenzae* which are resistant to streptomycin, e.g., retain their sensitiveness to sulfonamides, and there is a better chance of eliminating the infection completely if both drugs are administered.

P. W. C.

[4] DEMEREC, M.: Production of staphylococcus strains resistant to various concentrations of pencillin, Proc. Nat. Acad. Sci., 1945, xxxi, 16.

REVIEWS

Practical Physiological Chemistry. By PHILIP B. HAWK, Ph.D., President, Food Research Laboratories, Inc., BERNARD L. OSER, Ph.D., Director, Food Research Laboratories, Inc., and WILLIAM H. SUMMERSON, Ph.D., Associate Professor of Biochemistry, Cornell University Medical College. Twelfth Edition. 1323 pages; 23.5 × 16 cm. 1947. The Blakiston Company, Philadelphia. Price, $10.00.

The twelfth edition of *Practical Physiological Chemistry* follows the eleventh after 10 years and marks the fortieth year since the first edition by Hawk and Bergheim. Two new authors, Oser and Summerson, have joined the senior author with this edition and a group of authorities in various biochemical fields has assisted in the revision of the material in a number of chapters.

The past 10 years have been characterized by many advances in biochemical fields. Many of these are reflected in the revisions and additions to the clinical and theoretical aspects of the subject as well as in the choice of technical material. About half of the 36 chapters have undergone major revisions and one new chapter on antibiotics has been added. Much of the obsolete material has been deleted and new sections have been added on Warburg tissue slice technic, on the polarograph, electrophoretic fractionation of proteins, photometric and fluorimetric analysis and microbiological estimation of various amino acids and vitamins. The volume has been increased in size by over 350 pages.

The section on methods is good. Usually a number of alternate procedures are presented for the determination of a substance. Occasionally, however, a single method, not always too well known, is given alone. The appendix contains useful information of the preparation of solutions; tables on the composition of foods; and a section on the care of animals for nutritional experiments.

This edition should enjoy the same popularity as earlier ones, both as a textbook and as a reference volume for the clinical laboratory.

M. A. A.

Clinical Hematology. By MAXWELL M. WINTROBE, M.D., Ph.D., Professor of Medicine, University of Utah School of Medicine. 2nd Edition. Illustrated with 197 engravings and 14 plates, 10 in color. 862 pages; 24 × 15.5 cm. 1946. Lea & Febiger, Philadelphia. Price, $11.00.

There is no doubt that this volume is well on its way to establishing itself as a classic text in its field. The second edition, released for publication in October, 1946, displays evidence of careful revision throughout. The few years intervening between publication of the first edition and the present one have seen many important advances in hematology, most of which are accorded scholarly and comprehensive consideration here. Among the new material is an account of the discovery of the chemical structure, synthesis and use of "folic acid"; consideration of the implications and use of the nitrogen mustards in the lymphomata and leukemias; the rôle of the Rh factor in the etiology of erythroblastosis fetalis and hemolytic transfusion reactions. An entirely new chapter dealing extensively with the chemical metabolism of the erythrocyte and related pigment metabolism has been added. A feature of great value to the reader interested in pursuing a particular topic is the extensive and well-chosen bibliography. The book is highly recommended.

M. S. S.

Methods of Vitamin Assay. Prepared and Edited by THE ASSOCIATION OF VITAMIN CHEMISTS, INC. 189 pages; 23.5 × 16 cm. 1947. Interscience Publishers, Ltd., London. Price, $3.50.

"Methods of Vitamin Assay" is the result of the efforts of a group of chemists who formed an Association of Vitamin Chemists in 1943. Their aim was to promote "(1) the exchange of information on methods of vitamin analysis for specific food, feedstuffs, and pharmaceutical products; (2) the consideration of means of improving vitamin methods from the standpoint of cost, simplicity, and optimum correlation with the vitamin requirements of man; (3) a better interpretation of the significance of vitamin values, as determined by various methods." Members of this group together with other authorities submitted information on analytical technics, both published and unpublished, to a general methods committee who then chose one general method for each type of analysis which could be applied to the vitamin to be determined. These procedures are given in great detail with the assumption that they are to be carried out by laboratory technicians with a limited training in quantitative analysis. Procedures for vitamin A, carotene, riboflavin, niacin and ascorbic acid are given. References to methods for 10 other vitamins are also included.

Although many of the methods are applicable to the analysis of blood and urine, specific modifications are not always included in the extensive notes. This somewhat limits the usefulness of the methods for the usual hospital technician. The volume should prove invaluable, however, to all those interested in vitamin assay, and it should do much to standardize the methods of sampling and vitamin analysis of food and pharmaceutical products.

M. A. A.

BOOKS RECEIVED

Books received during June are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

Atlas of Cardiovascular Diseases: Correlation of Clinical Electrocardiography and Cardiac Roentgenology with Clinical History and Autopsy Findings. By IRVING J. TREIGER, M.D., Assistant Professor of Medicine, University of Illinois, Chicago, etc. 180 pages; 30 × 22 cm. 1947. The C. V. Mosby Company, Saint Louis. Price, $10.00.

Curare: Its History, Nature and Clinical Use. By A. R. MCINTYRE, Ph.D., M.D., Professor of Physiology and Pharmacology, College of Medicine, The University of Nebraska. 240 pages; 24.5 × 17.5 cm. 1947. The University of Chicago Press, Chicago. Price, $5.00.

Diagnosis and Treatment of Diarrheal Diseases (The). By WILLIAM Z. FRADKIN, A.B., M.D., Assistant Attending Gastroenterologist, Jewish Hospital of Brooklyn, etc. 254 pages; 23.5 × 16 cm. 1947. Grune & Stratton, Inc., New York. Price, $6.00.

Gynecology, With a Section on Female Urology (2nd Edition). By LAWRENCE R. WHARTON, Ph.B., M.D., Assistant Professor of Gynecology, The Johns Hopkins Medical School, etc. 1027 pages; 25 × 16.5 cm. 1947. W. B. Saunders Company, Philadelphia. Price, $10.00.

Health and Rehabilitation Through Chest Training. By SAMUEL DELANO, A.B., M.D., Harvard. 142 pages; 22.5 × 14.5 cm. 1947. The William-Frederick Press, New York. Price, $2.50.

Manual of the Common Contagious Diseases (A) (4th Edition). By PHILIP MOEN STIMSON, A.B., M.D., Associate Professor of Clinical Pediatrics, Cornell University Medical College, etc. 503 pages; 20 × 13.5 cm. 1947. Lea & Febiger, Philadelphia. Price, $4.00.

Methods of Diagnosis. By LOGAN CLENDENING, M.D., F.A.C.P., Late Professor of Clinical Medicine and History of Medicine, University of Kansas School of Medicine, and EDWARD H. HASHINGER, M.D., F.A.C.P., Professor of Clinical Medicine, University of Kansas School of Medicine. 868 pages; 25 × 17.5 cm. 1947. The C. V. Mosby Company, Saint Louis. Price, $12.50.

Microbial Antagonisms and Antibiotic Substances. (Revised Edition.) By SELMAN A. WAKSMAN, Professor of Microbiology, Rutgers University, etc. 415 pages; 24.5 × 16 cm. 1947. The Commonwealth Fund, New York. Price, $4.00.

Office Immunology, Including Allergy: A Guide for the Practitioner. Edited by MARION B. SULZBERGER and RUDOLPH L. BAER. 420 pages; 21 × 14.5 cm. 1947. The Year Book Publishers, Inc., Chicago. Price, $6.50.

Paravertebral Block in Diagnosis, Prognosis, and Therapy: Minor Sympathetic Surgery. By FELIX MANDL, M.D., F.I.C.S., Professor of Surgery, Hadassah University Hospital, Jerusalem. Translated by GERTRUDE KALLNER, M.D. 330 pages; 23.5 × 15.5 cm. 1947. Grune & Stratton, Inc., New York. Price, $6.50.

P–Q–R–S–T: A Guide to Electrocardiogram Interpretation (2nd Edition). By JOSEPH E. F. RISEMAN, M.D., Associate in Medicine, Harvard Medical School, etc. 84 pages; 14.5 × 21.5 cm. 1947. The Macmillan Company, New York. Price, $3.50.

Rocky Mountain Conference on Infantile Paralysis. Sponsored by THE UNIVERSITY OF COLORADO SCHOOL OF MEDICINE AND HOSPITALS and THE NATIONAL FOUNDATION FOR INFANTILE PARALYSIS, INC. 199 pages; 27.5 × 21.5 cm. (Paper). University of Colorado, School of Medicine and Hospitals, Denver. Price, $1.25.

Vascular Disorders of the Limbs, Described for Practitioners and Students (2nd Edition). By SIR THOMAS LEWIS, C.B.E., F.R.S., M.D., D.Sc., LL.D., F.R.C.P., Physician in Charge of Department of Clinical Research, University College Hospital, London, etc. 118 pages; 22.5 × 15 cm. 1947. The Macmillan Company, New York. Price, $2.25.

Psychiatric Research. Papers read at the Dedication of the Laboratory for Biochemical Research, McLean Hospital, Waverley, Massachusetts, May 17, 1946, by CECIL K. DRINKER, JORDI FOLCH, STANLEY COBB, HERBERT S. GASSER, WILDER PENFIELD and EDWARD A. STRECKER. 113 pages; 22 × 14.5 cm. 1947. Harvard University Press, Cambridge. Price, $2.00.

COLLEGE NEWS NOTES

Research Fellowships—The American College of Physicians

The American College of Physicians announces that a limited number of Fellowships in Medicine will be available from July 1, 1948–June 30, 1949. These Fellowships are designed to provide an opportunity for research training either in the basic medical sciences or in the application of these sciences to clinical investigation. They are for the benefit of physicians who are in the early stages of their preparation for a teaching and investigative career in Internal Medicine. Assurance must be provided that the applicant will be acceptable in the laboratory or clinic of his choice and that he will be provided with the facilities necessary for the proper pursuit of his work.

The stipend will be from $2,200 to $3,000.

Application forms will be supplied on request to The American College of Physicians, 4200 Pine Street, Philadelphia 4, Pa., and must be submitted in duplicate not later than November 1, 1947. Announcement of the awards will be made as promptly as is possible.

Autumn Meeting, Board of Regents and Committees

The regular autumn meeting of the standing committees and of the Board of Regents of the College will be held at the College Headquarters, Philadelphia, November 22–23, 1947.

The Committee on Credentials will consider only those candidates who have been formally proposed and their credentials completely filed sixty days in advance thereof, or by September 23.

All other matters requiring the attention of the Board of Regents should be submitted adequately in advance of November 21.

Committee on Masterships Appointed by the President

Among the amendments to the By-Laws adopted at the 28th Annual Session of The American College of Physicians, was one providing for a Committee on Masterships to be named by the President for the specific purpose of making nominations of Masters to the Board of Regents for election or rejection. The Mastership Committee shall consist of two members from the Board of Regents and one member from the Board of Governors. President Hugh J. Morgan has announced the appointment of the following Mastership Committee:

William S. Middleton (Chairman), Madison, Wis.
Walter B. Martin, Norfolk, Va.
Lewis B. Flinn, Wilmington, Del.

A Master shall be one who has attained the rank of Fellow and who on account of personal character, positions of influence and honor, eminence in practice or medical research, or other attainments in science or in the field of medicine, is recommended to the Board of Regents for special and well-earned distinction.

Eastern Pennsylvania Regional Meeting

The annual Regional Meeting for Eastern Pennsylvania members of the College will be held in Philadelphia, Friday, November 21, under the direction of Dr. Edward L. Bortz, Governor. The program will be announced later, but the meeting will be held in conjunction with a postgraduate course in Gastro-enterology to be given in

Philadelphia from November 17 to 26 under the auspices of the College, with Dr. Henry L. Bockus as Director. Luncheon will be served at the College Headquarters, and the afternoon and evening sessions will be held at the Warwick Hotel, 17th and Locust Streets, Philadelphia.

Nebraska Regional Meeting

The annual Regional Meeting for members of the College in Nebraska will be held at Lincoln on September 20, under the Governorship of Dr. Joseph D. McCarthy, F.A.C.P., Omaha. Members of the College from Lincoln will act as hosts. The program of the meeting will be printed and distributed to members throughout the state about the first of September.

Marking the twentieth anniversary of the founding of Georgia Warm Springs, a three-day clinical conference on diagnosis and treatment of poliomyelitis will be held at Warm Springs, Georgia, on September 15, 16, and 17.

Physicians interested in attending this conference should make inquiries to the Georgia Warm Springs Foundation, 120 Broadway, New York 5, N. Y. Complete program of the meeting will be available on request.

Second Annual Postgraduate Course in Diseases of the Chest

The American College of Chest Physicians is sponsoring a second annual postgraduate course in diseases of the chest to be held during the week of September 15–20, 1947, at the Municipal Tuberculosis Sanitarium, Chicago, Illinois. The emphasis in this course will be placed on the newer developments in all aspects of diagnosis and treatment of diseases of the chest.

The course will be limited to 30 physicians. Tuition fee is $50.00. Further information may be secured at the office of the American College of Chest Physicians, 500 North Dearborn Street, Chicago 10, Illinois.

The American Association for the Study of Goiter, of which Dr. James H. Means, F.A.C.P., Boston, is President, will hold its 1948 meeting at the King Edward Hotel, Toronto, Can., May 6, 7, and 8, 1948. The program will consist of papers dealing with goiter and other diseases of the thyroid gland, dry clinics and demonstrations.

Major General Norman T. Kirk, (MC), USA, F.A.C.P., and former Surgeon General, has been awarded the Typhus Commission Medal in recognition of the outstanding contributions he made to the work of the Commission.

Dr. Paul R. Hawley, F.A.C.P., Medical Director of the Veterans Administration, is the recipient of the Gorgas Award for 1947. This award, sponsored by Wyeth, Inc., is presented each year to a physician who has contributed signally to the field of military medicine.

The Distinguished Service Medal has been bestowed on Dr. Hawley for his exceptionally effective activities as Chief Surgeon in the European Theater of Operations, June, 1944, to May, 1945.

Dr. J. C. Geiger, F.A.C.P., San Francisco, has been honored by the award of the Crown of Orange Nassau, Officer Grade, by the Queen of Holland.

Brigadier General Edward A. Noyes, (MC), USA, F.A.C.P., has received the Legion of Merit for his successful development of special facilities for the care and

rehabilitation of patients while Service Command Surgeon of the Fifth Service Command, July, 1944, to September, 1945.

Colonel Edgar E. Hume, (MC), USA, F.A.C.P., is a recipient of the Typhus Commission Medal, given in recognition of his meritorious service during the 1943–44 epidemic of typhus in Naples.

The Legion of Merit has been awarded to Colonel William D. Graham, (MC), USA, F.A.C.P., to note his exceptional accomplishments as Commanding Officer of the 158th General Hospital, England, November, 1944, to July, 1945.

Captain Louis H. Roddis, (MC), USN, F.A.C.P., has been awarded the Navy Commendation Ribbon. The citation mentions his "invaluable consultation service," and his achievements in "disease prevention and evacuation of the sick and wounded."

Dr. Matthew Molitch, F.A.C.P., Atlantic City, N. J., and formerly Lieutenant Colonel in the A.U.S., is a recipient of the Army Commendation Ribbon. The citation refers to Dr. Molitch's contributions to the service while neuropsychiatric consultant at Fort Knox, January, 1944, to January, 1946.

Lieutenant Colonel Wayne G. Brandstadt, (MC), USA, F.A.C.P., has been awarded the Bronze Medal for his superior achievements in the management of battle casualties while Commanding Officer of the 53rd General Hospital, England, August 1, 1944, to May 8, 1945.

The Typhus Commission Medal has been given to Dr. David H. Clement, F.A.C.P., New Haven, Conn. Formerly a Major in the A.U.S., Dr. Clement is said to have improved methods of treatment of typhus fever while Surgeon in charge of the Commission's ward in the 116th Evacuation Hospital, Dachau, Germany, May–June, 1945.

Colonel William B. Foster, (MC), USA, (Associate) has been awarded the Legion of Merit for his exceptional accomplishments as a member of the Secretary of War's Separation Board, January, 1944, to February, 1946.

On June 30, Dr. Francis G. Blake, F.A.C.P., 2nd Vice President of the American College of Physicians, retired from the Deanship of the Yale University School of Medicine. His successor is Dr. C. N. H. Long, Sterling Professor of Physiologic Chemistry.

Dr. John D. Van Nuys has been appointed Dean of the Indiana University School of Medicine.

Dr. Robert C. Page, F.A.C.P., New York, N. Y., has recently given the College a copy of "A Biometric Study of Ten Years Medical Service," published as Number 1, Volume 7, of The Medical Bulletin by Standard Oil Company (New Jersey) and Affiliated Companies.

Dr. William C. Menninger, F.A.C.P., Topeka, Kans., has been elected to the position of President-elect of the American Psychiatric Association.

Proposed Army Medical Research and Graduate Training Center

The Army is planning to build a large medical center at Forest Glen, Md., outside Washington, D. C. It will comprise an Institute of Pathology building, a 1,000-bed general hospital, an Institute of Medicine and Surgery building, laboratory buildings, and an administration building which will contain an auditorium, research library and teaching facilities, as well as the Army Medical Museum. The Institute of Medicine and Surgery building will house the departments of Research Medicine, Research Dentistry, Veterinary Medicine, Research Surgery, X-Ray and Radiation, and Preventive Medicine. The plans include provisions for an animal farm and quarters for the staff.

Various Army units, now located elsewhere, will be brought to this center: the Medical Nutrition Laboratory, from Chicago; the Medical Field Research Laboratory, from Fort Knox; and the Surgical Research Unit, from Fort Sam Houston.

The hospital will have 200 of its 1,000 beds specifically allocated to research, and is so planned as to be capable of expansion to provide 1,500 beds.

The initial cost of the center is estimated to be $40,000,000.

University of California Medical School Offers Postgraduate Course in Psychiatry and Neurology

Dr. Stacy R. Mettier, F.A.C.P., Head of Postgraduate Instruction, Medical Extension, University of California Medical School, San Francisco 22, Calif., announces that a postgraduate course in psychiatry and neurology will be offered at the Langley Porter Clinic of the University of California Medical Center for a period of twelve weeks, September 8 to November 28, 1947. Instruction will be under the direction of Dr. Karl M. Bowman, professor of psychiatry in the University of California Medical School.

Registration is open to graduates of approved medical schools, and the number of registrants will be limited to sixty. Fee, $200.

Correction

In figure 1, page 192, of the article "Medicine in the European Theater of Operations" by Dr. William S. Middleton (February 1947 issue), the name of Lt. Colonel Benjamin H. Rutledge was inadvertently omitted from the list of Hospital Center Consultants by the author who has requested that this note of correction be made.

MINUTES, BOARD OF GOVERNORS

CHICAGO, ILL.

APRIL 28, 1947

The first meeting of the Board of Governors during the 28th Annual Session of the American College of Physicians convened at the Palmer House, Chicago, at 5:00 p.m., April 28, 1947, with Dr. C. W. Dowden, Chairman, presiding, and Mr. E. R. Loveland acting as Secretary. The following members were in attendance:

Oliver C. Melson	Arkansas
Ernest H. Falconer	California (Northern)
Benjamin F. Wolverton	Iowa
Edgar Hull	Louisiana
Douglas Donald	Michigan
Edgar V. Allen	Minnesota
Ralph Kinsella	Missouri
Harry T. French	New Hampshire
George H. Lathrope	New Jersey
Paul F. Whitaker	North Carolina
Robert B. Radl	North Dakota
Hugh A. Farris	Maritime Provinces
Arthur T. Henderson	Quebec
E. Dice Lineberry	Alabama
Fred G. Holmes	Arizona
Lewis B. Flinn	Delaware
Turner Z. Cason	Florida
Samuel M. Poindexter	Idaho
Walter L. Palmer	Illinois (Northern)
C. W. Dowden (Chairman)	Kentucky
Eugene H. Drake	Maine
Wetherbee Fort	Maryland
John G. Archer	Mississippi
Ernest D. Hitchcock	Montana and Wyoming
Asa L. Lincoln	New York (Eastern)
Joseph N. Ganim (Alternate)	Ohio
T. Homer Coffen (Alternate)	Oregon
M. D. Levy	Texas
Karver L. Puestow	Wisconsin
Ramon M. Suarez	Puerto Rico
John W. Scott	Alberta, British Columbia, Saskatchewan and Manitoba
Leland P. Hawkins	California (Southern)
W. B. Yegge (Alternate)	Colorado
A. B. Landry (Alternate)	Connecticut
Wallace M. Yater	District of Columbia
Cecil M. Jack	Illinois (Southern)
Harold H. Jones	Kansas
Chester S. Keefer	Massachusetts
Joseph D. McCarthy	Nebraska
Edward C. Reifenstein, Sr.	New York (Western)
Wann Langston	Oklahoma

Edward L. Bortz (Vice Chairman)	Pennsylvania (Eastern)
R. R. Snowden	Pennsylvania (Western)
John L. Calene	South Dakota
Louis E. Viko	Utah
Henry C. Gotshalk (Alternate)	Hawaii
Herbert K. Detweiler	Ontario
Gilbert M. Stevenson	Republic of Panama and the Canal Zone
Ex Officiis:	
Col. H. C. Dooling (Alternate)	United States Army
Adm. C. A. Swanson	United States Navy
O. L. Anderson (Alternate)	United States Public Health Service

Abstracted minutes of the previous meetings of the Board of Governors were read by the Secretary, and approved as read.

Chairman Dowden addressed the board briefly, reminding the members that he had circularized the entire Board by letter concerning the proposed amendments to the By-Laws affecting the eligibility of new members, and having received no replies, he felt justified in assuming that the Board of Governors wholly agreed to the proposed changes.

The Secretary, Mr. Loveland, read several communications from Governors who were unable to be present due to unusual circumstances. The death of Dr. J. O. Arnson, Governor for North Dakota, was noted, and the Board arose and observed a moment of silence.

The Secretary reported on proceedings of the Board of Regents at its meeting the day previous, covering those points of particular interest to the Board of Governors. These included: first, an amendment to the By-Laws providing that the maximum tenure of office of a Governor in the future shall be three terms of three years each; second, revision and restatement of the requirements for membership, with particular reference to Associates who fail to complete the requirements for Fellowship in the specified period of five years. There followed a general discussion of the subject of tenure of office of Governors, during which it was brought out that the new rules will probably be retroactive, and that none of the present Governors shall serve a longer period than three consecutive full terms of three years each; also that short terms as Acting Governors, or partial terms to fill out the unexpired term of a former Governor, will not be counted against the three full terms to which the incumbent may be entitled.

At this point, Dr. Wolverton discussed the manner of the election of Governors, suggesting that the American College of Physicians had never presumed to be a strictly democratic organization, but that the Fellows in any territory concerned should be polled in order that they may have some opportunity to express a preference for the Governor of their region. It was pointed out that the Nominating Committee is instructed by the By-Laws to give due consideration to suggestions of members from the respective states, provinces or districts, which will be represented by nominees if elected. Dr. Wolverton, however, felt that a definite routine should be established by which there would be an actual poll of the members in each state, the preference of each individual Fellow to be sent to the Executive Secretary, and the results turned over to the Nominating Committee to be used as a guide in making nominations.

Dr. Allen proposed that the Fellows in any state should have the right to elect by ballot their Governor, and that the members of the Board of Regents be elected by the Board of Governors; also that the President and Officers of the College likewise, by the Board of Governors. He felt this would bring the College in line with the truly representative organization that he felt it should be. He felt the present mechanism of merely allowing the Fellows to make recommendations to the Chairman of the Nominating Committee is a long way removed from a truly democratic system.

Chairman Dowden pointed out that this would entail a change in the By-Laws, and expressed a desire to have Dr. Wolverton and Dr. Allen submit their resolutions in writing, whereupon they will be presented to the Board of Regents for consideration, or to be more clearly presented to the Board of Governors for recommendation to the Board of Regents.

Dr. Levy, Governor for Texas, pointed out that in that state, where they have from 250 to 300 members scattered over a vast territory, it would be difficult for the men to select candidates, due to the isolation of one group from another, and the absence of any fairly intimate acquaintanceships over the state as a whole. He did not feel that a poll of the members by mail would produce the results desired. Such a plan had already been resorted to in some instances, and instead of getting any clear-cut selections of candidates, there has been a large number of candidates suggested, and in some instances, members have proposed their own names as candidates.

Dr. Palmer proposed, if this plan shall be tried, that they use the so-called Hare System, by which the complete list of Fellows would be furnished to the men in a particular state, and they would be asked to make nominations. There could be ten or fifty such nominations, and this list again may be sent to the same Fellows with the request that they vote in the order of first preference.

Dr. Holmes said that this method was used in elections in the Kiwanis Club for years, for the election of President, and that it necessitated polling several times. Dr. Holmes proposed that three top men for election would be more practical.

In extended discussion, a motion was made by Dr. Levy, and seconded by Dr. Hull, to proceed according to the various discussions advocated by Drs. Wolverton and Allen; Dr. Kinsella asked specifically for the wording of the motion, and the clarification of the statements therein. The reporter read the discussion, but confusion still remained, and many Governors expressed fear that any proposal, unless clearly worded and carefully organized, would lead to political manipulation in the election of the Officers, Regents, and Governors of the College.

Eventually, all motions were withdrawn, and Dr. Whitaker moved that a committee of five be appointed by the Chairman of the Board of Governors to study and to bring in some procedure for election of the members of the Board of Governors that will be satisfactory to the group as a whole.

The motion was seconded by Dr. Fort, put to vote, and carried.

Chairman Dowden appointed Dr. Allen, Chairman, Drs. Wolverton, Palmer, Levy, and Hull, and asked them to bring in their report at the next meeting of the Board of Governors.

Dr. Wolverton asked for some guidance, inquiring whether Associates should or should not have a voice in the election of Governors. It was pointed out by the Secretary that the By-Laws of the College definitely state that an Associate occupies purely a probationary status, and is entitled to no vote.

Chairman Dowden called upon Mr. Loveland to present the report of the Executive Secretary. Mr. Loveland stated that his full annual report would be given at the general business meeting of the College later in the week, and that since all Governors presumably will be in attendance, he would not repeat that portion of his report concerning finances, regional meetings, the Annals, membership data, etc.

He reminded the Board that the names of all candidates elected to Associateship or Fellowship had already been posted on the bulletin board; he discussed the problem of getting proposals filed adequately in advance—at least thirty days before action is required, and reminded the Board that under the new regulations, this period of time would be extended in the future to sixty days. He assured the Board that they would receive individual reports on all candidates who had been deferred or rejected. He explained that it had not been possible to publish a new and complete Directory of the College, due to paper and labor shortages, and excessive costs. In its place, a new Membership Roster had been published during January, 1947, and subject to the advice of the Board of Regents, a complete Directory would be published in the future.

The report of the Executive Secretary was accepted by resolution.

Dr. E. L. Bortz, Chairman of the Advisory Committee on Postgraduate Courses, reported that during 1946, the College conducted 23 postgraduate courses, with a total registration of 1,208 physicians, chiefly members of the College. He said the courses have been growing in popularity, and there has been a substantial improvement in the caliber of teaching. Whereas some years ago the Committee often had difficulty in interesting teachers and faculties of medicine to put on these courses for the College, his Committee now receives many offers from top flight individuals and institutions to participate in the College program. An attempt has been made to place the College courses at points over the country where the faculties are adequate to the needs of the College. The College has been as generous as possible with non-members in permitting them to attend the courses, but the demand from members in many instances has exhausted the facilities, and non-members could not be accommodated.

Dr. Bortz said the Committee considers the ideal size for the course to be 25 to 35, but the demand for the College courses has been so great that the size of the classes has had in many instances to be doubled or tripled. Some courses are already subscribed to one or more years in advance.

Dr. Bortz reviewed the proposed courses for the autumn of 1947 and the spring of 1948. He reported that the Committee, with the approval of the Board of Regents, had increased the registration fee from $20 to $30 per week, $25 of which will be turned over to the director or institution, and $5 of which will be withheld to be used by the College to help defray administrative expenses of arranging the courses. He emphasized also that the Committee proposes to have more instruction in the basic sciences than heretofore, and to enter into the newer work in the field of nucleolar physics and radioactive materials, etc. Dr. Bortz further reported that several other medical organizations have consulted the Committee and the Executive Secretary, considering ways and means of employing our type of program. He said it is significant that many faculties of medicine are leaning to this type of instruction, which concentrates material in such a way that men can get a great deal in a very short period of time.

(On motion by Dr. Allen, seconded and regularly carried, the report of the Advisory Committee on Postgraduate Courses was accepted.)

The Secretary, Mr. Loveland, reported that the Committee on Credentials had recommended to the Board of Regents and the Board of Regents had approved a new system of receiving votes from Fellows on new candidates, supplanting the card inquiry system in use for many years. The new plan provides that proposals shall be filed at least 60 days in advance of action; that the names shall be submitted in a geographical printed roster of candidates to all Fellows and Masters of the College, with requests for reports, whether favorable or unfavorable, on each candidate from the Fellows' or Masters' territory. The card system had become top-heavy, he said, in that it required the distribution of between 50,000 and 75,000 cards per annum, for which both forward and return postage was required, and with much expense involved for printing, filing, and so forth. The new system will provide a far more effective, less expensive, and more adequate plan, it was claimed by the Committee on Credentials.

In the discussion that followed, it was pointed out that this system does not in any way interfere with the present routine of many Governors, by which a consulting committee is maintained to help advise the Governor before he endorses a candidate. The appointment of such consulting committees is a matter that is entirely in the hands of the Governor, for his personal guidance. Information received through the card inquiry system, and sometimes on proposal forms themselves, often proved inadequate. Dr. Lathrope of the Committee on Credentials appealed to the Governors to take more care in seeing that full and complete data concerning every candidate's background,

experience, present appointments, and present activities, are always recorded for the assistance of the Committee on Credentials.

Chairman Dowden made an announcement concerning the agenda of the next meeting of the Board and other matters that should be submitted to the Governors for consideration.

Adjournment—6:20 p.m.

Attest: E. R. LOVELAND
Secretary

MINUTES, BOARD OF GOVERNORS

CHICAGO, ILL.

APRIL 30, 1947

The second meeting of the Board of Governors during the 28th Annual Session of The American College of Physicians convened at the Palmer House at 1 p.m., April 30, 1947, with Dr. C. W. Dowden, Chairman, presiding, and Mr. E. R. Loveland acting as secretary. The following were in attendance:

Oliver C. Melson	Arkansas
Ernest H. Falconer	California (Northern)
Benjamin F. Wolverton	Iowa
Edgar Hull	Louisiana
Douglas Donald	Michigan
Edgar V. Allen	Minnesota
Ralph Kinsella	Missouri
Harry T. French	New Hampshire
George H. Lathrope	New Jersey
Paul F. Whitaker	North Carolina
Robert B. Radl	North Dakota
Alexander M. Burgess	Rhode Island
Robert Wilson, Jr. (Alternate)	South Carolina
Paul K. French	Vermont
J. Edwin Wood, Jr.	Virginia
Charles E. Watts	Washington
Delivan A. MacGregor	West Virginia
Arthur T. Henderson	Quebec
E. Dice Lineberry	Alabama
Fred G. Holmes	Arizona
Lewis B. Flinn	Delaware
Turner Z. Cason	Florida
Samuel M. Poindexter	Idaho
Walter L. Palmer	Illinois (Northern)
C. W. Dowden (Chairman)	Kentucky
Eugene H. Drake	Maine
Wetherbee Fort	Maryland
John G. Archer	Mississippi
Ernest D. Hitchcock	Montana-Wyoming
Robert O. Brown	New Mexico
Asa L. Lincoln	New York (Eastern)
Joseph N. Ganim (Alternate)	Ohio
T. Homer Coffen (Alternate)	Oregon
M. D. Levy	Texas
Karver L. Puestow	Wisconsin
John W. Scott	Alberta, British Columbia, Saskatchewan and Manitoba

Leland P. Hawkins	California (Southern)
W. B. Yegge (Alternate)	Colorado
A. B. Landry (Alternate)	Connecticut
Wallace M. Yater	District of Columbia
Cecil M. Jack	Illinois (Southern)
Harold H. Jones	Kansas
Chester S. Keefer	Massachusetts
Joseph D. McCarthy	Nebraska
Edward C. Reifenstein, Sr.	New York (Western)
Edward L. Bortz (Vice Chairman)	Pennsylvania (Eastern)
R. R. Snowden	Pennsylvania (Western)
John L. Calene	South Dakota
William C. Chaney	Tennessee
Louis E. Viko	Utah
Henry C. Gotshalk (Alternate)	Hawaii
Herbert K. Detweiler	Ontario
Gilbert M. Stevenson	Republic of Panama and Canal Zone
Ex Officiis:	
Col. H. C. Dooling (Alternate)	United States Army
Capt. Frederick L. McDaniel (Alternate)	United States Navy
O. L. Anderson (Alternate)	United States Public Health Service
David P. Barr, President	
E. R. Loveland, Executive Secretary	

Reading of the minutes of the previous meeting was dispensed with.

CHAIRMAN DOWDEN: The President of the College, Dr. Barr, needs no introduction; we shall be happy to hear from him now.

PRESIDENT BARR: We had an opportunity to discuss our problems at the combined dinner meeting of the Regents and Governors on Sunday evening. I have nothing special to bring before you today.

Certainly no one can attend meetings such as we held in Philadelphia last year or the one we are having now without realizing the tremendous educational influence which this College has and can have. Many of us have the opportunity to see and to advise young men who want to be internists and who are arranging their entire lives for the next several years along the pattern which will enable them to qualify for certification and for Fellowship in this College. It goes farther than that. It is my belief that the internists are key people in the practice of medicine. Surgeons, in general, are pretty well occupied with technical procedures, also, general practitioners, as everyone knows; but internists, as a group, perhaps, do have a little more time to consider large problems of progress; they are interested in the broader phases of medicine.

I have had a growing realization of the tremendous responsibilities of this College. Now more than ever before, I feel this. The responsibility is something more than the mere setting of standards, or certification, or what we outline in black and white for preparation, but for positive education, for improvement of conditions of practice, for the better training of young men, for the enlarging of opportunities in residency. I am convinced that this is chiefly in the hands of the College. If the intent of the College is to be applied to the men who are going to be internists in this country, our influence must be exerted wholly.

The position of Governor has changed remarkably during the past few years, for at first it was more or less formal. The Governor's responsibilities, however, have rapidly expanded—he is responsible largely for new members; for advice in regard to certification; organization of regional meetings with their greatly increasing influence, etc. I think we are ready now to give more impetus to the work of the

Governor and the work in local districts to make the College work of a more positive educational value. The local or state meetings not only have the purpose of educating the Fellows who are present but extending certain training to men who will become Fellows later on.

I need not say that it has been a pleasure to be President of this organization; it has been a great privilege and a great honor and I shall retire with much greater convictions than I have had before of the great influence which the College has and can have. (Applause)

At this point, Chairman Dowden called on Dr. E. V. Allen, Chairman of the Committee appointed at the previous meeting, to give a report on proposals affecting the method of elections of Officers, Regents and Governors.

DR. ALLEN: This matter is a question of a more positive voice in the election of Governors by the Fellows in the respective states and territories. A motion was made at the last meeting of this Board, and withdrawn, that Governors be elected by direct vote of the Fellows of their geographic components. So much objection and discussion followed that the matter was referred to this Committee. The Committee has considered the matter at length. The first aspect of it is that there should be no change; the present situation is entirely satisfactory. The Committee itself is unanimous in the belief that the present situation is not satisfactory. The problem was then considered relative to the direct election of the Governor by the Fellows in his state or territory and it was felt that that was too great a step to take at the present time to have the support of the Committee.

Other alternatives were proposed. One was that the Fellows should be polled with regard to nominations of Governors, and the three names receiving the greatest number of votes should be submitted to the Nominating Committee for selection of a candidate.

The second alternative was that the Chairman of the Nominating Committee present to the Fellows of the various geographical components the names of three Fellows, and that the Fellows, themselves, would then select a Governor.

However, after consideration of these proposals in some detail, the Committee felt that the steps proposed should not be taken hastily; that we are not yet in shape to make a firm recommendation relative to this matter. Therefore, the Committee presents the following resolution:

"Whereas, It is desirable that the Fellows of The American College of Physicians of each State, District or Territory should have a voice in the selection of their Governor; and

"Whereas, The By-Laws (Article I, Section 3), provide that the selection of nominees for the Board of Governors shall be made after due consideration of suggestions of members; and

"Whereas, The Chairman of the Board of Governors has appointed a Committee to consider the problem in the foregoing; and

"Whereas, Said Committee has met in session; and

"Whereas, It is the opinion of the Committee that more time is needed for adequate study; and

"Whereas, A change should not be made hastily and without consideration of the many factors involved; be it therefore

"Resolved, That the Chairman of the Board of Governors designate the present Committee or appoint a new Committee to study the problem with diligence and care and make appropriate recommendations to the Board of Governors, whereby the above mentioned By-Laws may be implemented; said recommendation to be presented to the Board of Governors meeting in session in 1948."

Mr. Chairman, I will move the adoption of this Resolution.

DR. CASON: I second the motion.

CHAIRMAN DOWDEN: The matter is open for discussion.

DR. YATER: Does the adoption of this Resolution preclude any form of democratic polling of members of a district by the Governor should he wish to attempt to submit some names for the consideration of the Nominating Committee?

CHAIRMAN DOWDEN: I think any information a Governor can give to the Nominating Committee will have weight. This present Committee should be continued, to make a further report in 1948.

DR. ALLEN: It is the hope of this Committee that it will receive an expression from the Governors and I think it would be wise for the Governors to take a formal or informal poll of their membership relative to what they desire. I wish to emphasize this is not required by the By-Laws, although there is a By-Law already set up for this, and so no change in the By-Laws is contemplated at all.

DR. LATHROPE: The question brought up at our previous meeting was on the basis of democratization of the College. Personally, I feel this College cannot be a pure democratic organization. Five thousand men scattered all over North America cannot do it. To my mind, it should be an autocracy, but we should have a little better machinery for controlling the autocratic set-up. The crux of this problem goes right straight to the Nominating Committee. I would like to recommend to this Committee, which I think is a very good Committee and an important one, the consideration of a recommendation in a change in the By-Laws regarding the Nominating Committee. At present, in Section 3, Article I "Duties of the President: 'He shall within one month after induction to office appoint two members from the Board of Governors, two members from the Board of Regents and one Fellow at large'." to form a Nominating Committee. There you have a tight-fisted, closed organization about which you can do nothing should a group want to take control.

Now, we haven't had that yet. We have had a splendid organiation as long as I have known anything about the College, but it is right down the line. My suggestion would be that the Nominating Committee be an elective one; two members to be elected by the Board of Governors; two members to be elected by the Board of Regents; and they shall choose the fifth member.

DR. BURGESS: I should like to uphold the remarks of Dr. Lathrope. I think he has the right idea and this, followed out, will answer many of our objections, and still will not precipitate us into the troubles that we might get into if this matter were thrown open to allow for the political manipulations that in some areas would follow. I, therefore, urge that this special Committee give this suggestion consideration.

DR. BORTZ: A few years ago I was Chairman of the Nominating Committee, and we had a representative Committee. At no time was any member of the Committee approached by any member of the College to use his influence in any way in the selection of any nominee, either for the office of President or any of the other offices. I happen to know from members of other Nominating Committees, since then, that the Committees have been absolutely free of any approach by Officers of the College. They may have been approached by Fellows of the College with suggestions, but I think that sometimes the impression gets around that the President may appoint his friends on the Nominating Committee and that they hold a little secret conclave concerning who is to be nominated for office. I want to say that you can wipe that right off the slate, gentlemen, because any such impression is absolutely wrong.

I happen to know, also, that there have been Fellows of the College ambitious to become appointees to certain positions and that they have directly or indirectly approached certain members of the College and requested them to use their influence. That automatically removed that individual from any consideration of any nomination that the Nominating Committee might make. So, with all the faults and weak-

nesses, the Nominating Committee has not done too bad to date. I will say further that members of the Nominating Committee of which I was Chairman unofficially inquired around how various Fellows felt concerning proposed nominations. Not all Fellows in a particular region were polled, but there was a spot opinion obtained before the Committee went on record. Furthermore, the Committee made it a point to obtain the records of all proposed nominees, to study the records, the candidates' local positions with the Fellows, contributions to the College, etc. Observation of these men, their activities and participation in the work of the College after election, proved that the Committee was not far wrong in their selection. I would like to cite that a member of the Nominating Committee, when I was Chairman, who had served on other Nominating Committees and other positions, especially remarked that his experience with the College was extremely remarkable because no one was trying to manipulate the Committee. According to my experience, I cannot conceive of any nominations being conducted more fairly.

DR. LATHROPE: Mr. Chairman, I disclaim all criticism of anything that has gone on in the past. This organization has been carried on in a splendid and high-minded way up to date, but I am looking forward to twenty-five years from now when the College may have ten or twelve thousand members and might get into trouble then.

I would like to make another point: as a rule Fellows of the College are not too familiar with the responsibilities of the Governor, nor with the workings of the College. With a definite limitation on the term a Governor can serve, there will be every few years quite a good many new Governors elected to this Board. Would it not be a good thing for the new Governor to be elected a year preceding his taking office so that the man still in office can instruct him a bit in some of the details?

DR. WOLVERTON: Having started this original discussion, I should like to remark that I didn't mean democratization of the College from top to bottom; I had no such thought. I like to treat the College not as an autocracy but as a true aristocracy. The Fellows who control are the best men, and they control the best activities of the College and are the best men for that purpose. That is exactly as it should be. All that I had in mind was some mechanism whereby the Fellows in the respective geographical units would have more voice in indicating their preference for Governor so that there would be greater unanimity in the respective units and, perhaps, a better spirit.

DR. YEGGE: I am just an alternate Governor but it would seem to me that it would be a bit embarrassing to the Governor and to the members if he, himself, were to poll the state concerning his successor. If a state is to be polled, it should be done by the central office.

(The Resolution was put to vote as originally made by Dr. Allen's Committee and was carried.)

At this time, Chairman Dowden called for reports from Governors concerning their respective Regional Meetings during the past year.

Dr. Viko, Utah, had already reported on his meeting, March 29, before the Governors-Regents dinner meeting and had nothing to add.

Dr. Cason, Florida, reported a Regional Meeting held in Miami, November 3–4, 1946, in which the states of Alabama and Georgia participated. Dr. Cason asked that the new Governor for South Carolina contact him with a view to that state joining with the Southeastern states in their Regional Meetings. The Miami meeting had been well attended, the program was excellent and the results gratifying. Dr. Cason announced the next Regional Meeting for the area to be held in Tampa on or about December 5, 1947, that the plan of the meeting is being enlarged and on this occasion all Governors of the College will be especially invited, that a trip to Havana is planned immediately following the meeting in order to participate in the official formation of the new Cuban chapter of the College of which Dr. Centurion will be

named Governor. Dr. Cason said that a scientific program would take place on Monday and Tuesday and that the trip to Cuba should start on Wednesday. He further reported that the Governor for Puerto Rico had announced their state meeting there the following week and had extended an invitation to all Fellows interested to come to Puerto Rico from Cuba.

Dr. Fort, Maryland, reported the first tri-state Regional Meeting, Delaware, Maryland and District of Columbia, with invitations to West Virginia, North Carolina and Virginia, had been held at Baltimore, April 5, and through the coöperation of the University of Maryland and Johns Hopkins Hospitals, a most successful meeting had been held. The morning program was conducted at the University of Maryland Hospital, a luncheon was held at the Phipps Clinic Building at Johns Hopkins and the afternoon scientific session conducted in Hurd Memorial Hall at Johns Hopkins.

Dr. Lineberry, Alabama, reported that they had held their first Regional Meeting in Alabama at Birmingham on February 8, 1947. Not only had there been an excellent program, but the meeting contributed a great deal to broader acquaintanceships within the state. The scientific session had consisted of a series of fifteen-minute papers starting at 8:30 and concluding at 5:30 in the afternoon, followed by a dinner meeting. Dr. Lineberry advocated planning and announcing meetings earlier and also advocated that the state meetings be continued.

Dr. Walter L. Palmer, Northern Illinois, reported a Regional Meeting in Chicago on November 16, embodying Illinois, Indiana, Kentucky, Iowa, Michigan, Minnesota and Wisconsin. A wealth of material is available in that district, a most excellent scientific program was received with great enthusiasm and the attendance was between four and five hundred.

Dr. Reifenstein, Western New York, reported a Sectional Meeting of Western New York at Syracuse during the autumn of 1946; the meeting was well attended, the program well received. The Committee on Arrangements selected speakers primarily from the University of Buffalo, University of Rochester and the University of Syracuse. All the members had expressed the desire to have a Regional Meeting annually. He further stated that growing out of the experience of this Regional Meeting will be a request to have the territory of Western New York extended to include all of Northeastern New York down to and including Albany and following a border line from Albany to Binghamton, because all men in this territory will be more interested in the Regional Meetings in Western New York than in meetings held around New York City for Eastern New York.

Dr. Harry T. French, New Hampshire, reported that the New England Regional Meeting had been held at Hanover, New Hampshire, on January 28, 1947, with a gratifying program and attendance.

Dr. Paul K. French, Vermont, announced that the next New England Regional Meeting is being planned for Burlington in the autumn of 1948 and that invitations will be sent also to the Maritime Provinces and Quebec. Incidentally, Montreal is only one hundred miles removed from Burlington.

Dr. Chaney, Tennessee, reported a state meeting for Tennessee at Memphis on November 22, 1946. It was a one-day meeting at which several distinguished guests were on the program. The meeting proved exceedingly popular from the great host of letters of commendation received thereafter. Dr. Chaney said that the value of these meetings lies not only in their educational phase but in the opportunities presented to get acquainted with the internists in the whole region.

Dr. McCarthy, Nebraska, reported that several years ago state meetings were held immediately following the Annual Session of the College at which the meeting and important papers and clinics were reviewed. On March 29, 1947, the State of Nebraska held a state meeting at Omaha with every member in attendance with the exception of three. Prospective candidates for Associateship were invited to attend

as guests so that Fellows could observe them and get acquainted. A scientific session had been held in the afternoon, with papers presented by Fellows of the College who are on the faculties of the two medical schools. He advocated that these state meetings be used as a proving ground for younger men, both from the standpoint of the work they are doing and also the presentation thereof. Dr. McCarthy asked for advice with regard to whether the policy shall be to hold multi-state regional meetings or individual state meetings.

Chairman Dowden replied saying he felt it purely up to the state and the local circumstances. If a group of states desire to join, it is perfectly all right, or, if individual states desire to organize their own more personal meetings, it meets with the complete approval and coöperation of the College generally. However, the Board of Regents has been inclined to encourage the return to the state type of meeting rather than the extension of the very large multi-state regional meetings, except where special conditions warrant.

Dr. Bortz reported a meeting for Eastern Pennsylvania at Philadelphia on February 7, 1947, with the participation of members from New Jersey and Delaware, and with numerous guests from Western Pennsylvania and New York. He said that he feels the type of meeting, whether state or multi-state, depends upon the number of members available. States with small membership obviously should join with nearby territories, thus to make the meetings adequate. In Eastern Pennsylvania, Dr. Bortz uses the Regional Meeting as a proving ground for some of the younger members. Large committees of younger men are appointed and younger men of greater promise are placed on the program, especially Associates of the College. It gives them an opportunity to show what they are doing and also serves as a great stimulus, when they see that the College does not strictly limit its programs to the older men of great prominence and accomplishment. Incidentally, this gives the Governor a better knowledge of talent among the younger men and helps him in making recommendations to the Chairman of the Annual Session for papers from the local area. At the Philadelphia Regional Meeting, it has been customary to give a buffet luncheon, as a routine matter, to allow the visiting members to see and visit the College Headquarters. At the scientific program, Dr. Bortz usually asks other men to preside, men outside of the Philadelphia area, and in this manner, Fellows from other parts of the region feel that they become a more active part of the College. In the evening, the program is light and convivial, with no too serious talks. Every year the meetings are growing in size and popularity.

Dr. Whitaker, North Carolina, reported a Regional Meeting for that state at Winston-Salem on October 18, 1946. North Carolina has established the policy of alternating the meetings between Chapel Hill, where the University of North Carolina Medical School is located, and Winston-Salem, where the Bowman Gray School of Medicine is located. A five-man program committee is appointed annually and an attempt is made to establish membership interest throughout the state. Some meetings have taken the form of a symposium on certain phases of internal medicine while others have been didactic papers with clinics and demonstrations added. Furthermore, the state of North Carolina often joins the surrounding territories, such as the District of Columbia, Virginia and other states, in their regional meetings. Dr. Whitaker, too, inquired further about the policy of the College with regard to strictly state or multi-state meetings.

Dr. J. Edwin Wood, Jr., Virginia, reported a state meeting held at Richmond on February 19, 1947, which had been the best attended of any previous meeting. He advocated that the College or the Board of Governors formulate a definite policy with regard to the type of meeting to be held in the future, expressing the opinion that the type of meeting probably must be dependent somewhat upon the medical population of the state. In general, Dr. Wood felt that the individual state meetings, with the fellowship that goes with them, are the best type.

Dr. John Archer, Governor for Mississippi, reported that the State of Mississippi has only twenty members of the College and that heretofore they have been included within the Sectional Meeting for Tennessee, Arkansas, Louisiana and East Texas. In Mississippi, Dr. Archer has developed the plan of having an annual luncheon at the annual Mississippi State Medical Society meeting. At these luncheons practically all Mississippi members of the College are in attendance. A guest speaker is engaged and, in some instances, this guest speaker has been the College Governor for one of the neighboring states. Such a luncheon meeting was planned during the Mississippi State Meeting at Biloxi in May, 1947. The luncheons afford an opportunity for the members to get together, to know each other better and to discuss younger men in the state who may be aspiring to Associateship.

Dr. E. Dice Lineberry, Governor for Alabama, at this point, pointed out that some of the larger sectional meetings might be revised to advantage with respect to their territories, providing the organizing Governor's feelings would not be hurt. In the case of Alabama, the members had found it a little more convenient and attractive to attend the Sectional Meeting at Memphis rather than join in the Sectional Meeting in Florida.

An inquiry was made as to whether or not there are any states or provinces which are not included in some regional meeting set-up, and the Secretary, Mr. Loveland, reported that there are several such states and provinces not yet so included.

Chairman Dowden pointed out that there is nothing compulsory about a state or province holding a regional or sectional meeting, that if a small state with only a few members doesn't want to have a state meeting, it is not compelled to do so. The College, however, hopes that there will be enough interest manifested for some type of regional get-together once a year. Dr. Dowden did not think it appropriate for the College to dictate specific policy, but each Governor should be guided by what the majority of his members desire. In Kentucky, the members during the war and up to the present time had been joining with the large multi-state meeting for the Midwest region embodying Illinois, Indiana, Iowa, Michigan and Wisconsin, but very few of the Kentucky members had attended, whereas when Kentucky holds its own state meeting, ninety-five per cent of the members attend, which obviously is much to be preferred.

Dr. Joseph D. McCarthy, Governor for Nebraska, still advocated some expression of policy as to what these meetings shall be for and the form in which they shall be conducted. He asked whether the Governors are trying to put on minor annual meetings or are trying to accomplish other work within their individual states. He referred to the very large population of the College included in the Midwest Regional Meeting and intimated that the purpose of these large meetings, obviously, will be much different from the small, more personalized state meeting.

Dr. Walter L. Palmer, Governor for Northern Illinois, stated that when organizing his last meeting, he had consulted the Governors in the neighboring states to determine whether or not they, without obligation of any sort, wished to join in the large regional meeting at Chicago, and all of them voted to do so, whether wisely or unwisely. He stated further that he had called a meeting of all of the Governors concerned for a conference the day following this meeting of the Board of Governors to discuss again the question of whether the policy of joining together on this regional meeting shall be continued. He intimated that while it might be definitely desirable in Nebraska to have the restricted state meeting for the purposes previously suggested by Dr. McCarthy, it might not be feasible in a large populated area like Northern Illinois where the members are, to some extent, reasonably well known to one another. He pointed out that Chicago, for instance, is divided into four different medical school groups, a number of hospital staffs, with one society, the Chicago Society of Internal Medicine, to which most of the College Fellows in the area belong, and this society

conducts monthly meetings which provide an opportunity for the members to become acquainted. Dr. Palmer further felt that the type of multi-state regional meeting held in his area in no sense competes with the Annual Session because it is quite different in character. The local regional meeting program consists of fifteen-minute presentations largely by local, younger men. He expressed the opinion that the demands on the Annual Session program, including clinics, panel discussions, morning lectures, etc., are so great that a regional meeting program could in no sense compete.

Dr. R. R. Snowden, Governor for Western Pennsylvania, reported a Regional Meeting for that district had been held on September 11, 1946, during a postgraduate course in internal medicine conducted on the College program. During the war, Western Pennsylvania had joined up with Ohio and West Virginia in holding combined regional meetings which were not too well attended. Local Fellows had found the more personal, local meeting more stimulating and beneficial, with the result that Western Pennsylvania has been gratified to return to the purely local type of meeting where interests are common, where acquaintanceships are renewed, where a great deal of enthusiasm in the College is aroused and where younger men, interested in the College, may be invited as guests.

Chairman Dowden said that the deliberations and discussions of the Governors would be referred to the Board of Regents to see if that Board wishes to express any opinion or policy with regard to regional meetings.

Dr. George H. Lathrope, by resolution, was re-appointed a member of the Committee on Credentials from the Board of Governors for a three-year term, expiring 1950.

Chairman Dowden opened the meeting to a general discussion of policy with regard to the future of the College, character of the meetings, etc.

Dr. Lathrope stated that the question of increasing membership in the College is becoming acute. With continued growth, there is likely to develop difficulty in finding cities with adequate facilities to accommodate our present type of Annual Meeting. He suggested an amendment should be made to the By-Laws requiring that a candidate shall be thirty-five years of age before election to Associateship. He explained that while this appears radical, his experience on the Survey Committee of the College a year ago convinced him that there is a gradually sinking importance of the College as compared with the gradually rising importance, in the eyes of the young doctors, of the American Board. He cited a case where a Fellow recommended a young man for Fellowship recently wherein the recommendation referred only to the fact that he had passed his American Board examinations, and, therefore, is now "perfectly eligible" for Fellowship in the College. He emphasized, of course, that this is not what the rules and regulations of the College provide.

Dr. Burgess rose in support of Dr. Lathrope's point of view, to point out that if the age limit for entering Fellowship is thirty-eight or more, that would automatically make the age limit for Associateship as thirty-five, which, in his opinion, would be desirable. Dr. Burgess cited a recent instance which occurred at a meeting of the American Board of Internal Medicine in which the members felt that that organization, which is a creation of this College and has been made strong by the College requiring certification as one of its prerequisites, has now become almost too strong in position. Some members of the Board of Internal Medicine would agree that, in the minds of the young internists, too preponderant importance is given to the Board. He felt that Fellowship should be made a greater honor, more desirable and more selective. The College would advance in this direction, he thought, by adopting some general regulation as suggested by Dr. Lathrope; that certification should be required early, as a basis on which to build for qualification for Fellowship in the College. Certification, he said, should be a starter, showing that a man is qualified to be a specialist in internal medicine, but Fellowship in the College should show that he has fully qualified and has become a distinguished specialist.

Dr. E. V. Allen took the opposite point of view and expressed the belief that the purpose of the College should not be to recognize training, merit and experience. He felt that if the College has a function, it should be in the encouragement of attainment and education among younger men. He would be very reluctant, he said, to see the College became a group of middle-aged and older men who have achieved some prominence or eminence, a sort of old man's club, its chief function being to put its stamp of approval on a stage of respectability and merit. He felt it should be emphasized that the function of the College is that of education, that membership should not serve as a reward for attainment but as encouragement for attainment, encouragement for young men to strive for the things for which the College stands—scholarship, personal relations between the doctor and his patients and his associates. With regard to the American Board of Internal Medicine, Dr. Allen felt that there is no need for fear about its increasing importance since its function is only that of setting its stamp of approval on the training of an individual.

Dr. Edgar Hull likewise expressed opposition to any age limit for membership in the College, but suggested the possibility of lengthening the period allowable for Associateship in the College, thus not denying younger men the stimulation of junior membership in the College.

Dr. Cason said he would like to demonstrate democracy in action. He referred to at least two professors in medical schools who are under thirty years of age; while exceptions might be made for such men, it must be admitted that youth has brains. He stated that much of the fault in the increasing membership of the College is that of the Governors—that too many Governors endorse candidates whom they know are inadequately qualified. Too many candidates are "accommodated" when a careful analysis would show that their credentials are not up to the standards the College should expect. He cited cases of candidates for Associateship coming up at the age of forty-eight and fifty, men who had never previously thought of entering the College and who are definitely borderline cases. He thought Governors too often endorse ill-qualified candidates because they fear criticism of other Fellows. He referred to an early Convocation address made before the College when the speaker talked about autocracy and said that when the College grows too big, it would lose its importance and influence. Dr. Cason bespoke a plan which would become more selective but not be limited by age.

Dr. Allen, at this point, emphasized the fact that the Credentials Committee has the opportunity and the authority to determine the size of the College because it, in the final analysis, selects those who are elected.

Dr. Palmer expressed the opinion that the basic aspect of the problem, as previously touched upon by Dr. Hull, lies in the changing nature of the practice of medicine; that the general practitioner is doomed to extinction; that the specialist is going to have more and more his day. He emphasized the importance of seeing that the general practitioners of the future are well and thoroughly trained, and he asked whether The American College of Physicians is to consist only of the elite of that group and what shall be its criterion.

Dr. Snowden discussed a growing trend in some regions of institutions requiring staff members not only to be certified by the American Board of Internal Medicine, but also Fellows of The American College of Physicians. He thought that probably explains the reason why some internists now fifty or more years of age, faced with this problem suddenly, start attempting to qualify for Fellowship in the College. He thought it acceptable that certification be required but was inclined to suggest that Governors of the College discourage institutions, both teaching and hospital, from requiring Fellowship in the College as a prerequisite for staff membership. He felt that Fellowship in the College should be more than a stamp of approval that may be required by some hospital or teaching institution.

Dr. Burgess said it is the unanimous opinion of members of the American Board of Internal Medicine that a hospital which requires certification for promotion on a staff is not living up to its own responsibilities; the hospital should be able to judge its own members for advancement and should not put any such problem up to any board anywhere. Dr. Burgess then, referring to previous discussions by Dr. Allen, decried any attempt to "pass the buck" from the Board of Governors to the Credentials Committee in regard to the selection of candidates. He felt it the function of the Board of Governors to make the most careful selection of candidates before individual Governors shall endorse them and send their credentials to the Committee. A Governor has a greater opportunity to investigate a candidate in his own state and among his own Fellows than has a small Credentials Committee acting for the country at large. He urged Governors to be thorough and specific in their recommendations to the Credentials Committee.

Chairman Dowden asked the Board, and particularly Dr. Lathrope, if any particular action were desired—some resolution, the appointment of a committee to study the problem further and report back later.

Dr. Lathrope thought that no particular resolution was required because the purpose of the original discussion was to air the situation generally and to obtain the opinions of the individual members of the Board. He felt the discussion had been exceedingly helpful and productive of much good not only among the Governors but among the members of the Credentials Committee.

CHAIRMAN DOWDEN: "The time has come when the Board must consider the election of a new Chairman. I should like to express my appreciation of your courtesy and of your support and patience. I have appreciated your unfailing courtesy, your support and your attendance at our meetings."

In the regular manner prescribed by the By-Laws, Dr. Walter L. Palmer was elected Chairman of the Board of Governors for a three-year term, expiring in 1950. Dr. Palmer responded, expressing his deep appreciation of the honor and assuring the Board of his greatest efforts to uphold the duties of the office and to maintain the splendid record set by the retiring Chairman, Dr. Dowden.

Dr. Allen, on behalf of the Board of Governors, rose to express to the retiring Chairman "our gratitude and our true affection for the Chairman we have had for the past few years." (All members of the Board arose and applauded.)

Dr. Allen introduced the recommendation that the meeting time of the Board of Governors should be carefully studied with a view to arranging a schedule at the next Annual Session by which the meetings would not conflict with the scientific program and by which the Governors might have more adequate time for their deliberations. He suggested the possibility of meeting during the forenoon of the first day or some other acceptable arrangement.

It was pointed out that the Secretary, Mr. Loveland, is also Secretary of the Board of Regents, the general business manager of the Annual Session, and that the schedule heretofore has been worked out in such a manner as to enable him to perform his duties as required under the By-Laws.

Dr. Yater suggested the possibility of the Board having its first meeting on Tuesday evening when there is no other conflicting event. Obviously, the Board of Governors cannot meet at the same time as the Board of Regents because not only is Mr. Loveland the Secretary of each Board, but the Chairman of the Board of Governors is also a member of the Board of Regents.

On motion by Dr. Allen, seconded by Dr. Yater and regularly carried, it was resolved that the Chairman and the Executive Secretary be requested to arrange a better meeting time for the Board of Governors to allow for longer and adequate discussions.

Adjournment—3 p.m.

Attest: E. R. LOVELAND
Secretary

OBITUARIES

DR. F. WARNER BISHOP

Dr. F. Warner Bishop, of New York City, died in St. Luke's Hospital on March 23, 1947.

Dr. Bishop was born in Brooklyn, N. Y., on April 18, 1887. He received his academic and medical training at Columbia University, from which he received the B.S. and M.D. degrees in 1910 and 1912. Most of his medical life was devoted to St. Luke's Hospital where, at the time of his death, he was an Attending Physician. From 1936 to 1938 he served as President of St. Luke's Medical Board. He at one time held appointments as Instructor in Physiology and in Clinical Medicine in Columbia University.

Dr. Bishop was a member of the Medical Societies of the State and County of New York; of the New York Academy of Medicine; the New York Clinical Society, of which he was formerly President; and of the American Heart Association. He had been a Fellow of the American College of Physicians since 1937.

Dr. Bishop was a very highly respected member of the medical profession and a skilled physician.

ASA L. LINCOLN, M.D., F.A.C.P.,
Governor for Eastern New York

DR. JOHN LEONARD KANTOR

Dr. John Leonard Kantor, a leading gastro-enterologist of New York City, died at Mt. Sinai Hospital, June 25, 1947.

Dr. Kantor was born in Moscow, Russia, on April 12, 1890, and came to this country the following fall. He attended Columbia University, receiving the degree of Bachelor of Arts in 1908, and the M.D. and Ph.D. degrees four years later. He then served a three-year internship in the Mt. Sinai Hospital, and entered the Army Medical Corps as a specialist in gastro-enterology during the First World War.

Dr. Kantor became associated with the faculty of the Columbia University College of Physicians and Surgeons in 1916 and rose to the position of Associate Clinical Professor of Medicine. From 1919 to 1935 he was on the staff of the Vanderbilt Clinic, where he served as Chief of the Clinic of Gastrointestinal Diseases. He also served as Associate Roentgenologist at the Montefiore Hospital for Chronic Diseases, as Gastro-enterologist at the Beth David Hospital, and as Consultant in gastrointestinal diseases to the Will Rogers Memorial Hospital, Saranac Lake, N. Y., the National Jewish Hospital, Denver, Colo., and the Sharon (Conn.) Hospital.

During World War II, Dr. Kantor saw active service in New Guinea as Chief of the 49th General Hospital.

Dr. Kantor was a member of the New York Academy of Medicine and of the New York Gastro-enterological Association, of which he was a former President. He was also a member of the American Medical Association, the American Roentgen Ray Society, the Association of Military Surgeons of the United States, the Medical Societies of the State and County of New York, and of Phi Beta Kappa, Sigma Xi, Alpha Omega Alpha, Phi Delta Epsilon. A Diplomate of the American Board of Internal Medicine, Dr. Kantor was elected to Fellowship in the American College of Physicians in 1938.

His premature death means a real loss to the medical profession of New York City.

ASA L. LINCOLN, M.D., F.A.C.P.,
Governor for Eastern New York

DR. WASHINGTON MERSCHER

Dr. Washington Merscher of Clifton Springs, N. Y., died suddenly on June 15, 1947. Dr. Merscher had just become a Fellow of the College, by direct election, on April 27, 1947.

Dr. Merscher was born December 9, 1888, at Philadelphia, Pa. He was graduated from the University of Pennsylvania School of Medicine in 1910. He interned in the Germantown Dispensary and Hospital and entered practice in Philadelphia. During his period of practice in that city, he served on the Medical Staffs of the Roxboro Memorial Hospital and the Germantown Dispensary and Hospital. From 1934 to 1937 he held appointments in the Temple University School of Medicine as Instructor in Medicine. In 1937, following an illness, he removed to Watkins Glen, N. Y., where he became Chief of the Medical Service of the Glen Springs Sanatorium. In 1943 he joined the staff of The Clifton Springs Sanatorium and Clinic as an internist.

Dr. Merscher was a member of the Ontario and the Schuyler County Medical Societies, New York; of the Medical Society of the State of Pennsylvania; and was a Fellow of the American Medical Association.

Dr. Merscher was recently the head of the Gastro-enterological Section at The Clifton Springs Sanatorium.

He was regarded by his associates as a very capable internist and was especially beloved by his patients because of his kindly manner and interest in them.

EDWARD C. REIFENSTEIN, M.D., F.A.C.P.,
Governor for Western New York

DR. WILLIAM TIMOTHY O'HALLORAN

Dr. William T. O'Halloran of Newtonville, Mass., died at his home on May 21, 1947, following a coronary thrombosis. At the time of his death he was Chief of the Sixth Medical Service of the Boston City Hospital and Assistant Professor of Medicine at Boston University School of Medicine.

Dr. O'Halloran graduated from Tufts College Medical School and joined the staff of the Boston City Hospital, where he advanced over the years from house officer to Chief of the youngest of the Medical Services of the hospital.

Dr. O'Halloran was a member of the Newton Medical Club, American Heart Association, New England Heart Association, Massachusetts Medical Society; was a Fellow of the American Medical Association and, since 1941, of the American College of Physicians. He was considered a skillful physician and loyal friend by his colleagues, and he commanded the respect of all who served with him.

CHESTER S. KEEFER, M.D., F.A.C.P.,
Governor for Massachusetts

DR. JOHN WILLIAM PRESTON

John William Preston, M.D., F.A.C.P., Roanoke, Va., died January 1, 1947, age 79 years. He graduated from the College of Physicians and Surgeons, Baltimore, in 1893. He pursued postgraduate work at the University of Pennsylvania, Harvard Medical School, the Johns Hopkins Hospital and at the University of London, in subsequent years. He became a member of the American Congress on Internal Medicine in 1921 and a Fellow of The American College of Physicians in 1922. He had been in the practice of internal medicine at Roanoke for many years. He was a Diplomate of the American Board of Internal Medicine and since 1917 had been the Secretary-Treasurer of the Virginia State Board of Medical Examiners. During World War II, he was Chairman of the Medical Advisory Board for Roanoke and a member of the Army Induction Board.

DR. HOWARD GUSTAV SCHLEITER

Dr. Howard Gustav Schleiter, F.A.C.P., of Pittsburgh, Pa., widely known cardiologist, died on February 5, 1947, after a brief illness. Born in Pittsburgh, May 27, 1880, he received his A.B. degree from Harvard College and M.D. degree from the University of Pennsylvania. After postgraduate work at Mt. Vernon Hospital and the University College Hospital, London, England, he devoted more and more of his time and energy to diseases of the cardiovascular system, in which field his knowledge, experience, and sound judgment were widely recognized.

Dr. Schleiter was for many years Visiting Physician to the St. Francis Hospital, and Associate Professor of Medicine in the School of Medicine, University of Pittsburgh. At the time of his death he was Chief of the Cardiological Service of the Allegheny General Hospital, and of the Pittsburgh Diagnostic Clinic. Dr. Schleiter was a Diplomate of the American Board of Internal Medicine.

He was a member and former President, Pittsburgh Academy of Medicine; member, Allegheny County Medical Society, Pennsylvania State Medical Society, American Medical Association, American Clinical and Climatological Society, and the American Rheumatism Society; a Fellow of the American College of Physicians since 1930.

Dr. Schleiter was a man of wide cultural attainments. He was particularly interested in music and was himself a pianist of unusual ability. Widely traveled, with his broad education and intense interest in all the arts, a fluent and witty conversationalist, he was at all times an interesting and stimulating companion. His untimely death takes from us an able physician and an inspiring friend.

R. R. Snowden, M.D., F.A.C.P.,
Governor for Western Pennsylvania

DR. WILLIAM F. SCHROEDER

Dr. William F. Schroeder, F.A.C.P., of Rock Island, Ill., died on June 10, 1947.

Dr. Schroeder was born in Rock Island on September 24, 1885. He attended the University of Illinois, by which he was awarded the Degree of Bachelor of Arts, in 1909. During World War I, he served in the U. S. Army, and achieved the rank of Captain of Infantry. Subsequently Dr. Schroeder attended the University of Minnesota. The degrees of Bachelor of Science (1922) and Doctor of Medicine (1926) were conferred upon him by that institution.

Dr. Schroeder served as a member of the medical staffs of the Lutheran and Moline Public Hospitals, Moline, Ill.; of St. Luke's Hospital, Davenport, Iowa; and as former Chief of Staff of St. Anthony's Hospital, in Rock Island.

Dr. Schroeder was a member of the Illinois and Iowa State Medical Societies, and a past President of the Rock Island County Medical Society. He was a Fellow of the American Medical Association, and became a Fellow of the American College of Physicians in 1932.

Dr. Schroeder found legitimate pride in attempting to solve many problems that came to his patients, whether medical, social or economic. He was a kindly, understanding companion to all. His unfaltering loyalty to his patients and to the best interests in his profession will long be remembered.

Harry W. Shuman, M.D., F.A.C.P.

DR. GEORGE MUNRO GOODWIN

Dr. George Munro Goodwin, F.A.C.P., of New York City, died July 12, 1947, after a brief illness in St. Luke's Hospital. He was Director of Medicine in St. Luke's Hospital and Professor of Clinical Medicine in the College of Physicians and Surgeons of Columbia University.

Dr. Goodwin was born in Brooklyn, October 24, 1887, received his medical degree from Columbia University College of Physicians and Surgeons in 1911, and interned in St. Luke's Hospital, with which institution he has been associated for the past 36 years, having advanced through various grades until he was made Director of Medicine in 1945. He was also Consultant in Medicine at the New York Orthopedic Hospital.

In the early years of his practice, Dr. Goodwin was very closely associated with the late Dr. Samuel W. Lambert and with Dr. Henry W. Patterson. He was formerly President of the Medical Board of St. Luke's Hospital, a member of many medical societies, a Diplomate of the American Board of Internal Medicine and had been a Fellow of The American College of Physicians since 1937.

Dr. Goodwin was a specialist in internal medicine and perhaps will be remembered best as a teacher of medicine. His untimely death is a very distinct loss to the medical profession.

Asa L. Lincoln, M.D., F.A.C.P.,
Governor for Eastern New York